

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-499V

Filed: April 25, 2024

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JULIAN HENLEY,

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Petitioners,

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v.

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Ruling on Entitlement;
Hepatitis B (“Hep B”) Vaccine
Pemphigus Vulgaris

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SECRETARY OF HEALTH
AND HUMAN SERVICES,

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Respondent.

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Richard Gage, Esq., Richard Gage, P.C., Cheyenne, WY, for petitioners.

Colleen Hartley, Esq., U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT¹

Roth, Special Master

On April 22, 2016, Dr. Julian Henley (“Dr. Henley” or “petitioner”) filed a petition pursuant to the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*² (“Vaccine Act” or “the Program”). Petitioner alleges that the hepatitis B vaccination (“HBV”) that he received on April 3, 2015 caused him to develop painful lesions. Thereafter, petitioner was diagnosed with pemphigus vulgaris (“PV”). Petition at 1-2, ECF No. 1.

After carefully analyzing and weighing the evidence presented in accordance with the applicable legal standards, I find that petitioner has provided preponderant evidence that the HBV

¹ Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims’ website and/or at <https://www.govinfo.gov/app/collection/uscourts/national/cofc> in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

² The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) (“Vaccine Act” or “the Act”). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

vaccinations³ he received were a substantial factor in his development of PV, satisfying petitioner's burden of proof under *Althen v. Secretary of Health & Human Services*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). Accordingly, petitioner is entitled to compensation.

I. ISSUES TO BE DECIDED

Both parties agree that petitioner has pemphigus vulgaris and that he received the subject HBV vaccination on April 3, 2015. Pre-Hearing Joint Submission, ECF No. 102. Thus, petitioner's diagnosis is not at issue. The main issue in contention is "[w]hether petitioner's subject Hepatitis B vaccine caused-in-fact his pemphigus vulgaris pursuant to *Althen*." *Id.*

Petitioner asserts that he has met his burden under all three *Althen* prongs. Petitioner's Pre-Hearing Brief ("Pet. Br.") at 6-9, ECF No. 93. Respondent disagrees and argues that petitioner has "not provided sufficiently reliable evidence of causation to satisfy the elements of *Althen*." Respondent's Pre-Hearing Submission ("Resp. Br.") at 19-23, ECF No. 105.

II. BACKGROUND

A. Medical Terminology

Pemphigus is an autoimmune blistering disease caused by autoantibodies against desmogleins ("DSG") or epithelial intercellular components. Pet. Ex. 17 at 1;⁴ Pet. Ex. 18 at 1;⁵ Pet. Ex. 19 at 1.⁶ While its etiology is unknown, it is occasionally associated with antecedent medications, infections, or neoplasms and "has been reported to follow viral and bacterial vaccination." Pet. Ex. 19 at 1. *Kridin et al.* explains that "[t]he pathogenesis of the disease is mediated by IgG autoantibodies against desmoglein 3 (pemphigus vulgaris) and desmoglein 1 (pemphigus foliaceus), two trans-membrane desmosomal glycoproteins" that are cell-to-cell adhesion molecules. Pet. Ex. 18 at 1; *see also* Pet. Ex. 45 at 6.⁷ These autoantibodies inhibit the adhesion of desmogleins, leading to the loss of adhesion between keratinocytes resulting in blister formation through a process called acantholysis. Pet. Ex. 18 at 1. Pemphigus is the result of predisposing genetic and environmental factors. *Id.*

In lay terms, PV is an autoimmune disease, meaning the body attacks itself when it recognizes specific proteins as foreign and starts making antibodies against them. The proteins in PV are DSG 1 and 3. Tr. 112. These antibodies bind to the "adhesive proteins" or sticky substances

³ Although petitioner alleged only the third HBV vaccine as causal in his petition, his theory was in part based on challenge-rechallenge and his experts implicated all three HBV vaccines. For reasons discussed at length in this Ruling, I find preponderant evidence supports petitioner's theory of challenge-rechallenge involving the second and third Hepatitis B vaccines.

⁴ Yackov Berkun et al., *Pemphigus Following Hepatitis B Vaccination-Coincidence or Causality?*, 38 AUTOIMMUNITY 117 (2005), filed as "Pet. Ex. 17", "Pet. Ex. 30", "Resp. Ex. A Tab 3", and "Resp. Ex. C Tab 1".

⁵ Khalaf Kridin et al., *Is There an Association Between Pemphigus and Hepatitis Viruses? A Population-Based Large-Scale Study*, 65 IMMUNOLOGY RES. 1083 (2017), filed as "Pet. Ex. 18", "Pet. Ex. 31", "Resp. Ex. A Tab 4", and "Resp. Ex. C Tab 2".

⁶ C. De Simone et al., *Exacerbation of Pemphigus After Influenza Vaccination*, 33 CLINICAL AND EXPERIMENTAL DERMATOLOGY 718 (2008), filed as "Pet. Ex. 19", "Pet. Ex. 33", and "Resp. Ex. C Tab 3".

⁷ Mohsen Masjedi et al., *Cytokine Indexes in Pemphigus Vulgaris: Perception of Its Immunopathogenesis and Hopes for Non-Steroidal Treatment*, 16 IRANIAN J. OF PHARMACEUTICAL RES. 1223 (2017), filed as "Pet. Ex. 45."

which hold the skin cells together, and the result is the breakdown of tissues in the mucous membranes which includes the linings of the nose, mouth, throat, eyes, and certain genital surfaces, as well as blisters on the skin. It is a painful and terrible disease. Tr.112-13.

More recent literature provides that, “[w]hile pemphigus is an autoantibody mediated disease, the role of T cells and cytokines in the pathogenesis is being increasingly recognized”. Pet. Ex. 44 at 1.⁸ The loss of adhesion between keratinocytes is induced by autoantibody production associated with both Th1 and Th2 derived cytokines. Pet. Ex. 45 at 1.⁹ “The production of pathogenic antibodies is key to the development of blisters in pemphigus, and many immunological steps are required prior to autoantibody production.” Pet. Ex. 44 at 1. Mouse model experiments show that both DSG specific T and B cells are necessary to produce pathogenic autoantibodies, “and the role of T cell subsets and their cytokines is being increasingly recognized.” *Id.* Proinflammatory cytokines include IL-1, IL-8, and tumor necrosis factor. *Id.* at 1-2. Cytokines are likely the key players in the coordination of the cellular and humoral responses in pemphigus. *Id.* at 3-4.

B. Procedural History

An onset hearing was conducted on November 30, 2016. On March 9, 2017, I issued a Fact Ruling, finding that Dr. Henley began suffering from symptoms of PV in May of 2016, or within 4 weeks of his receipt of the third HBV vaccination. Ruling on Facts, ECF No. 32. The complete procedural history was included in the Ruling on Facts and is incorporated by reference herein. ECF No. 32.

Following the issuance of the Fact Ruling, the parties engaged in discussions to resolve the matter but to no avail. ECF Nos. 32-39. The parties then exchanged expert reports and filed medical literature. Pet. Ex. 15-23, ECF Nos. 42-43, 50, 52, 58; Respondent’s Exhibits (“Resp. Ex.”) A-H, ECF Nos. 45-47, 53-54, 59-60.

An Entitlement Hearing was conducted on July 22, 2021. Following the hearing, an Order issued for the filing of additional documentation referred to during the hearing. ECF No. 111. Those documents were filed while the parties resumed discussions to resolve the matter. Resp. Ex. I-O; ECF Nos. 112-13; Pet. Ex. 38-67, ECF Nos. 116, 120, 122, 126, 131, 135, 139-40, 145, 148-49, 154, 159, 164. The case was referred to ADR, which was ultimately unsuccessful. ECF No. 169, 177. An Order concluding ADR proceedings issued on June 29, 2023. ECF No. 177.

The matter is now ripe for entitlement.

C. Factual Background

A comprehensive medical history is contained in the Fact Ruling previously issued. *See* ECF No. 32. However, because of the rarity of PV, the subtleties of its presentation, and the arguments of the experts involving petitioner’s medical history and the events following each of his HBV vaccinations, the most pertinent medical history is repeated herein.

⁸ Sang Hee Lee et al., *Analysis of Serum Cytokine Profile in Pemphigus*, 29 ANNALS OF DERMATOLOGY 438 (2017), filed as “Pet. Ex. 44.”

⁹ Masjedi et al., *supra* note 7.

Petitioner is a board-certified head and neck surgery specialist. Fact Hearing (“FH”) Tr. 5. When he started working at Regional West Medical Center (“RWMC”), he was tested for and failed to show antibodies to hepatitis B and was required to take the hepatitis B (“HBV”) vaccine series. FH Tr. 5. Petitioner received the first of three HBV vaccinations on December 6, 2012. Pet. Ex. 5 at 1.

On February 19, 2013, petitioner presented to Platte Valley Dental Group (“Dental”) in Scottsbluff, Nebraska. Pet. Ex. 9 at 1. Heavy gingival bleeding was noted. A cleaning was completed with a hand instrument only. *Id.* It was recommended that he return in 6 months. *Id.*

Seventeen months later, on August 6, 2014, petitioner returned to Dental for crowns on teeth #29 and #31. Treatment for gum inflammation was discussed. Pet. Ex. 9 at 1. A return in three months was recommended but petitioner advised he could only schedule every six months due to his work schedule. *Id.*

Blood work performed at RWMC on September 4, 2014 again showed that petitioner did not have hepatitis B antibodies. Pet. Ex. 1 at 1. He received a second HBV vaccine on October 28, 2014. Pet. Ex. 5 at 1.

On April 3, 2015 petitioner received a third HBV vaccination.¹⁰ Pet. Ex. 5 at 1.

Two weeks later, on April 14, 2015, petitioner established care with a primary care physician (“PCP”). Pet. Ex. 2 at 1. He was noted to be a 67-year-old physician with prostate issues and lower leg swelling for the past 6-7 years. *Id.* He reported that a previous stress test and echocardiogram were normal; he had an appendectomy at age 9 and developed hepatitis resulting from a penicillin injection.¹¹ *Id.* at 1, 3. He had been diagnosed with hypertension and prescribed Lisinopril, but he developed angioedema and discontinued the medication, opting to follow a paleo diet and restrict salt intake. *Id.* at 1. He had no other symptoms. *Id.* Minor pitting edema of the legs was noted on examination. *Id.* at 2. The assessment was enlarged prostate, venous insufficiency, leg edema, and elevated blood pressure. *Id.* at 3. A family history of diabetes, lung cancer, colon cancer, gastrointestinal cancer, and hypertension was noted. Petitioner was prescribed Cialis for his enlarged prostate and stockings for vascular support. *Id.*

On May 15, 2015, a hepatitis surface antibody test was positive for immunity to hepatitis B. Pet. Ex. 1 at 9.

Two and half months after his third Hep B vaccination, on June 23, 2015, petitioner presented to his dentist with tender gums and bleeding on the top and bottom of the right side of his mouth. Pet. Ex. 9 at 2. Examination revealed severely red tissue with 5-6 mm pocketing. *Id.* A periodontal consult was recommended along with a return in three months and regular rinses with Peridex but petitioner was not interested. *Id.*

On June 28, 2015, petitioner had an emergency Dental visit due to severe pain and an abscess on tooth #29. Pet. Ex. 9 at 2. The tooth was treated with oral antibiotics and Peridex rinse

¹⁰ Petitioner alleged only that the April 3, 2015 HBV vaccine was responsible for causing his PV. *See* Petition at 1; Pet. Br. at 1-2.

¹¹ Petitioner testified to the sanitary conditions in Poland, where he was born and raised, and contracting hepatitis from needles that were reused at that time. FH Tr. 42-43.

was prescribed. *Id.* Final treatment for tooth #29 was performed on July 17, 2015. No other complaints were noted. *Id.*

Petitioner presented to the Eye Center of Northern Colorado (“Eye Center”) on August 17, 2015 for redness and irritation of his right eye. Pet. Ex. 7 at 9. He had tried multiple eye drops without improvement. *Id.* A clogged meibomian gland¹² and a hordeolum (stye)¹³ was noted; hot compresses and antibiotic drops (ciprofloxacin) were prescribed. *Id.* at 11.

Petitioner presented to his colleague, Dr. John Blomstedt at RWMC on August 24, 2015, for a chronic pruritic scalp rash that he was scratching constantly, lesions on his right lower eye lid and the right side of his nose. He had been using topical steroids, anti-fungals, and topical antibiotics without improvement. He requested biopsies. Pet. Ex. 3 at 1. Biopsies performed on the vertex of his scalp and right nasolabial fold were positive for pemphigus vulgaris.¹⁴ *Id.* at 1-3.

Petitioner returned to the Eye Center on August 27, 2015 because the lesion on his lower eyelid had not improved and was bothersome, despite warm compresses and antibiotic drops. Pet. Ex. 7 at 13. The appearance of the lesion that day was concerning for carcinoma. *Id.* at 15. A biopsy of the right lower eyelid showed extensive epidermal acantholysis with dyskeratosis¹⁵ raising concern for an acantholytic disorder, such as pemphigus. *Id.* at 1, 17.

Laboratory work on September 16, 2015 revealed very high serum levels for both Desmoglein 1 and 3.¹⁶ Pet. Ex. 1 at 13. Additional laboratory results from September 17, 2015 indicated that petitioner had normal levels of G6PD.¹⁷ *Id.* at 10.

Petitioner presented to the Dermatology Department at the University of Colorado Hospital (“Dermatology”) on September 24, 2015, “for evaluation of pruritic and painful rash of 2 months duration involving the scalp, face and chest. Lesions are crusted over. Rash is worsening over time.” Pet. Ex. 4 at 3. Use of topical steroids, antifungals, a Medrol dose pack, and Dapsone failed to result in improvement. *Id.* Skin biopsies performed at an outside clinic revealed extensive acantholysis with dyskeratosis consistent with pemphigus foliaceus.¹⁸ Labs sent to the Mayo Clinic were positive for DSG 1 and 3. *Id.* A shave biopsy performed on petitioner’s left shoulder was consistent with a type of pemphigus but did not clearly distinguish pemphigus vulgaris from

¹² The meibomian glands are sebaceous follicles between the tarsi and the conjunctiva of the eyelids. *Dorland’s Illustrated Medical Dictionary* 770, 773, 1108 (33rd ed. 2019) [hereinafter “*Dorland’s*”].

¹³ Hordeolum is also called a “stye” and is a localized, purulent, inflammatory staphylococcal infection of one or more sebaceous glands of the eyelids. *Dorland’s* 858-59.

¹⁴ Pemphigus vulgaris is the most common and severe form of pemphigus, characterized by chronic, flaccid, easily ruptured bullae on the skin and mucous membranes. It begins focally but then becomes generalized, leaving large, weeping, denuded surfaces that partially crust over but do not heal and enlarge by confluence. If left untreated, it may be fatal. *Dorland’s* 1384.

¹⁵ “Dyskeratosis” is the abnormal, premature, or imperfect keratinization of the keratinocytes, which are epidermal cells that synthesize keratin. Keratinocytes make up about 95 percent of the cells of the epidermis. *Dorland’s* 571, 967.

¹⁶ Desmogleins are the target of autoantibodies in pemphigus foliaceus and pemphigus vulgaris. *Dorland’s* 494.

¹⁷ G6PD stands for “glucose-6-phosphate dehydrogenase.” It is an enzyme of the oxidoreductase class that catalyzes the oxidation of glucose-6-phosphate to a lactone, reducing NADP⁺ to NADPH. The reaction is the first step in the pentose phosphate pathway of glucose metabolism. Genetic deficiency of the enzyme causes severe hemolytic crises in affected individuals. *Dorland’s* 781.

¹⁸ Pemphigus foliaceus is a mild but chronic form of pemphigus, characterized by small flaccid bullae that rupture and crust, as well as exfoliation. It may be limited to the scalp, face, and trunk or may become generalized. *Dorland’s* 1384.

pemphigus foliaceus. *Id.* at 4, 16. The assessment was “[l]ikely Pemphigus foliaceus...” *Id.* at 7. Petitioner was prescribed doxycycline, two infusions of rituximab, and continued use of Dapsone. *Id.*

Petitioner returned to Dermatology on October 22, 2015. It was determined that the pemphigus was more consistent with vulgaris due to oral involvement and DSG 3 positivity. The suspected trigger of the pemphigus was the HBV vaccination series given the time course. Pet. Ex. 4 at 22. “Since his last visit in 9/2015, patient has noted progression of disease with more erosions on the upper trunk and scalp, persistent enlargement of the periorbital erosions, and onset of erosions in the mouth along the buccal and lingual mucosae.” *Id.* Petitioner was noted to be “somewhat resistant to higher doses of prednisone as he is currently operating and is concerned about mood changes.” *Id.* at 23. “Symptoms started with erythema around a seborrheic keratosis on his upper chest following the second round of HBV series, but resolved within a few weeks. After receiving the third round in 7/2015, he noted diffuse onset of erosions on the scalp, face, and chest.^[19] He was previously treated with doxycycline, dapsone and systemic antifungals...” *Id.* On that date, petitioner had scattered erythematous crusted erosive macules and patches mostly on his upper trunk, right periorbital area, scalp, lateral neck, abdomen, and left medial orbital rim. *Id.* at 24. Erosions were also noted on the right posterior buccal mucosa and, to a lesser extent, the lingual and left buccal mucosa. *Id.*

That same day, Dr. Norris wrote a letter stating that petitioner was under his care for pemphigus vulgaris “suspected to be precipitated from hepatitis B vaccination.” Pet. Ex. 4 at 30. The letter further stated that petitioner was advised to remain at home for approximately one month until reevaluation, at which time further time off would be determined. *Id.*

Petitioner returned to Dermatology on November 25, 2015. It was documented that he had “pemphigus vulgaris with oral involvement and DSG3 positivity, suspected trigger likely HBV vaccination series given timecourse.” Pet. Ex. 4 at 35. Since his last appointment he had been on an increased dose of prednisone (60mg) and had received two Rituximab infusions. *Id.* Petitioner’s skin, eye, and oral lesions had improved. *Id.* Petitioner had self-tapered to 40mg of prednisone three days prior and was tolerating it well. *Id.* The plan was to taper prednisone and start a steroid sparing agent. *Id.* He was prescribed CellCept and instructed to continue “dexamethasone swish & swallow, silvadene, and topical steroids”. *Id.* He could return to work in January as long as the skin lesions were healed. *Id.*

Petitioner returned to Dermatology on December 23, 2015. The risk of immunosuppression was discussed due to his profession as a surgeon in an acute care setting where he was exposed to MRSA, CMV, and other infections. Pet. Ex. 4 at 51. Though he had no new lesions, he had some disruption of the skin barrier when the skin was stretched. *Id.* at 52. His right eye was improved; there was only a “single improving lesion” in his mouth. *Id.* Petitioner wanted to return to work but had developed tremors in his hands as a side effect of the high dose steroids, which would keep him from doing surgery. *Id.*

¹⁹ At the fact hearing, petitioner testified that the record incorrectly states the date of his third hepatitis B vaccination as 7/2015. FH Tr. 38-39. Petitioner testified that, when asked by the treating resident how long ago he had received the third hepatitis B shot, he had stated that it was several months ago or a few months ago. FH Tr. 38-39. However, other records confirm that petitioner received the third hepatitis B vaccine on April 3, 2015. Pet. Ex. 5 at 1.

The remainder of petitioner's records document his course of ongoing treatment for PV and other conditions he has developed.

D. Fact Witness Affidavits and Petitioner's Testimony

The affidavits of petitioner, the witnesses, and testimony of Dr. Henley from the Fact Hearing are detailed at length in the Fact Ruling but bear repeating in summary fashion because the details are relevant to the arguments made by the experts on entitlement.

a. Petitioner's Affidavits

Petitioner submitted two affidavits, one on June 15, 2016 and one following the Fact Hearing on October 21, 2021.

In his June 15, 2016 affidavit, petitioner affirmed receipt of three Hep B vaccinations on December 6, 2012, October 28, 2014, and April 3, 2015 at RWMC. Pet. Ex. 6 at 1.

Petitioner affirmed that he did not notice any reaction after the first vaccine, so, if present at all, it was minor. Following the second vaccine on October 28, 2014, he developed a rash on his chest that resolved on its own within weeks. Pet. Ex. 6 at 1.

Petitioner recounted arguing with RWMC about having a third vaccine when told that he had failed to develop antibodies after the second hepatitis B vaccine. He was told a third vaccine was required. He received the third vaccine on April 3, 2015. Pet. Ex. 6 at 1.

According to petitioner, within a week or two of the third hepatitis B vaccine, he developed bleeding from his gums when he brushed his teeth and several nose bleeds. Pet. Ex. 6 at 1. He assumed the gum bleeding was due to gingivitis and the need for a dental cleaning. *Id.* At the same time he noted some non-tender skin lesions on his scalp which he attributed to the surgical headlamp he wore. *Id.* He also had a sty on his right lower eyelid and a pimple-like lesion next to his nose. *Id.* at 1-2.

Petitioner affirmed that a dental cleaning failed to resolve the dental issues and he then developed an abscess for which he was given antibiotics. He ultimately had an emergency root canal. Pet. Ex. 6 at 2. Petitioner did not connect the dental issues with an autoimmune reaction. His dental issues distracted him from doing anything about the skin lesions, which were not painful at that time. *Id.* He recalled noting that the sty and skin lesions failed to respond to the antibiotics he took for the dental issue. *Id.*

Petitioner affirmed a visit to an ophthalmologist for the sty on his right eye and was told to put hot compresses on it. When that did not work, he was sent to an eyelid specialist who performed a biopsy. He then formally saw his colleague, Dr. Blomstedt, who took several biopsies, all of which came back suspicious for "pemphigoid autoimmune process." Pet. Ex. 6 at 2.

In hindsight, petitioner realized that the scalp lesions, eye lesion, and gum issues were all concurrent, and "...are recognized as early manifestations of [the] pemphigus autoimmune reaction". Pet. Ex. 6 at 2. The lesions evolved slowly and were not painful at the beginning. He added that making appointments with specialists takes time, so "there was a natural gap between the vaccination and the formal diagnosis of autoimmune pemphigus." *Id.* His insistence on biopsies accelerated the diagnosis. *Id.*

Following the Fact Hearing, petitioner submitted an affidavit clarifying his use of lisinopril. Pet. Ex. 43. Petitioner affirmed taking three doses of lisinopril in 2009, but it made him dizzy and caused his blood pressure to drop too low, so he stopped taking it. Pet. Ex. 43 at 1. In 2015, he took one dose when his blood pressure was high from pain but that night, he developed palatal swelling (angioedema), so he never took another dose. *Id.* He affirmed that he has not taken a single dose of lisinopril since that isolated episode in 2015. *Id.*

b. Petitioner's Testimony at the Fact Hearing

Petitioner testified at the fact hearing. Not all of his testimony is included herein but is contained in the Fact Ruling. ECF. No. 32.

Petitioner is a physician specializing in surgery of the head and neck. FH Tr. 5. He sees patients in a clinical setting for otolaryngology issues, as well. FH Tr. 5.

Petitioner's work schedule at the time of the vaccinations included alternating weeks between Scottsbluff, Nebraska and Colorado, where he divided his time between Fort Collins and Greeley. FH Tr. 67. As a trauma surgeon, he was on call at night in both Nebraska and Colorado when present in each of those states. FH Tr. 67-69. He would see patients in Scottsbluff during the day and was on call nights and weekends for trauma. FH Tr. 67-69. He then would drive back to Colorado on Monday morning or Sunday night, see patients and would be on call for trauma in Colorado. Scottsbluff was divided between him and Dr. Massey, who practices the same specialty. When petitioner was in Scottsbluff, Dr. Massey was in Mississippi; when Dr. Massey was in Scottsbluff, petitioner was in Colorado. FH Tr. 69. Petitioner was on call seven nights a week. FH Tr. 70.

Petitioner started work at RWMC in Scottsbluff, Nebraska in 2012. FH Tr. 5-6. Around that time, he received a letter from his employer stating that his blood work did not show antibodies to hepatitis B and that he would be required to take the Hep B vaccines. FH Tr. 5.

After the first HBV vaccine in 2012, petitioner developed a nonspecific rash on his chest that was not itchy or painful and went away on its own.²⁰ He attributed the rash to climate/location change and did not seek medical intervention. FH Tr. 6, 47. After the second vaccination, he developed a lesion on his left shoulder and asked his colleague Dr. Massey to do a biopsy because it was on a sun-exposed area, and he was concerned for basal cell carcinoma. FH Tr. 6-7. The redness disappeared the following week, so he never went for the biopsy. FH Tr. 7. Petitioner confirmed that there are no medical records for the rash on his chest or the lesion on his shoulder. FH Tr. 48.

Petitioner stated in early April 2015, he was informed that he needed a third hepatitis B vaccine because his blood work failed to show antibodies from the first two hepatitis B vaccines.²¹ FH Tr. 7. He recalled arguing with the nurse about receiving a third vaccine but was told that it was mandatory. FH Tr. 7. He was unaware if his concerns were documented. FH Tr. 48-49.

Approximately one month later, petitioner noticed a scabbing rash on the top of his head in the area where he wore his surgical headlamp. FH Tr. 8. He explained that his headlamp is

²⁰ Petitioner stated in his affidavit that he developed the rash on his chest after receiving the second hepatitis B vaccine. Pet. Ex. 6 at 1.

²¹ Petitioner's medical records reflect the testing was done on September 4, 2014, prior to the second HBV vaccine. Pet. Ex. 1 at 1.

mounted on his forehead by a band during surgery for 6 to 8 hours at a time; the rash started under the headlamp. He thought it was an allergic reaction to the plastic in the hardware. FH Tr. 8, 72. At the same time, he noticed bleeding when he brushed his teeth but assumed he needed a dental cleaning. He was also having nose bleeds. FH Tr. 8-9. There was also “a little sore on the bottom of [his] nose that looked like a pimple” and “some inflammatory changes on the eyelid that looked like a sty.” FH Tr. 11.

Petitioner did not mention the foregoing to his PCP on April 14, 2015, when he presented for prostate issues and swelling of his legs because he was more concerned that the ankle swelling could be an indication of a heart related issue. FH Tr. 50-51; Pet. Ex. 2 at 1-3. Petitioner did not recall his gums bleeding at that time, but since it was a visit with an internist, he probably would not talk about things not pertinent to the specific issue he was there for. FH Tr. 51. He added that he did not yet have painful skin lesions, and he did not recall having nose bleeds at that time. FH Tr. 51-52. Further, the sty was not visible yet. He first noticed it sometime in May. FH Tr. 71-72. He noticed the lesion on his nose around the same time as the eye and the scalp. FH Tr. 74.

He presented to the dentist on June 23, 2015. The record documents, “Gums are tender and bleeding on the right side, top and bottom.” FH Tr. 21; Pet. Ex. 9. He recalled the bleeding when he brushed and tenderness on the right side of his mouth going on for a while but thought it was his own negligence in dental care. Tr. 21-22. He increased flossing and used better cleaning habits for several weeks, but his gums continued to bleed that was when he made the dental appointment. FH Tr. 22, 24, 55-56. Despite his efforts, the gum bleeding got worse. FH Tr. 63. Because of his schedule and when he and the dentist would both be in Scottsbluff, it took until June 23, 2015 to coordinate an appointment. FH Tr. 10, 24, 55, 62-63.

Petitioner agreed that he had inflammation and gingivitis in past, but “...this time it was different. It was more localized to the right side; it was more painful; and the bleeding did not resolve with improved dental hygiene.” FH Tr. 55-56, 58. He then developed an abscess on the right side and needed an emergency root canal due to extreme pain, for which he could not take pain medication because he was on call for trauma. FH Tr. 44-45, 64-65. He stated that “...later ...when the tooth problem was over, I was able to really see a specific lesion on the right side...with a flashlight.” FH Tr. 75-76.

Petitioner stated that he performed a surgery with Dr. Blomstedt, who focuses on dermatology, around the time of his dental issues. FH Tr. 11-12. After the surgery, he stopped by Dr. Blomstedt’s office and asked him to look at his head. FH Tr. 11-12. Dr. Blomstedt thought it looked like a rash and gave petitioner some samples of steroid or antibiotic creams to try. FH Tr. 11, 16. Petitioner used the samples on and off for about a month and may have also used bacitracin on his own before that. FH Tr. 77.

Petitioner recalled the bleeding gums, nosebleeds, and scalp lesions all happening at the same time, but did not connect the dental issues with the skin lesions. FH Tr. 24, 56-57, 65. He also assumed the antibiotics prescribed by the dentist would work on the other inflammatory skin lesions which normally would have gotten better with antibiotics, but they did not; that was when he told Dr. Blomstedt that he needed biopsies. FH Tr. 65.

Petitioner stated the escalation of his symptoms was gradual; when the pain increased was blurry. But, by the time he realized he needed a biopsy, the scalp irritation had become lesions. FH

Tr. 77-78, 18. The eye lesion looked like a styne but got worse even with compresses. “[W]hen the eye lesion was going on for about six weeks, I finally broke down and I had an eye appointment.” FH Tr. 18-19.

Petitioner stated he first formally visited with Dr. Blomstedt was on August 24, 2015 so the biopsies could be done. Dr. Blomstedt’s record documents a “chronic rash on his scalp” because he had seen him for it before, informally. The record referenced the lesions on the right lower eyelid and the right side of his nose. FH Tr. 17, 53-54; Pet. Ex. 3 at 1. Biopsies were performed on his nose and scalp; both came back with a preliminary diagnosis of suspected autoimmune disorder. FH Tr. 19-21.

Around the same time, petitioner recalled seeing an ophthalmologist. When the prescribed ointment and compresses did not work, he was sent to an eyelid specialist, who did a biopsy of the eye lesion. FH Tr. 27-28. That biopsy came back as pemphigus as well. FH Tr. 28. At that point, three biopsies from three different sites, all had the same result. FH Tr. 28-29.

Petitioner went to the University of Colorado because no one at RWMC had experience with pemphigus. FH Tr. 25-26. On September 24, 2015, he presented to Drs. Norris and Caldwell at the University of Colorado. FH Tr. 26-27. The initial record documented a “67 [year old] Ashkenazi Jewish Caucasian male who comes to the clinic for the first time for evaluation of pruritic and painful rash of 2 months duration involving the scalp, face and chest.” FH Tr. 31-32; Pet. Ex. 4 at 3. Petitioner described the rash on his head as initially not painful, but over time it became so painful that it hurt to take a shower and could no longer be ignored. FH Tr. 32-33. He described his conversation with Drs. Norris and Caldwell as “fairly loose” explaining to them that “some months ago” he had a final hepatitis B booster shot then developed some rashes that were now painful. FH Tr. 33. Thinking back, it all started after the booster shot. Tr. 34-36.

Petitioner discussed his next visit on October 22, 2015 where the record reads, “[a]fter receiving the third round [of Hep B vaccines] in 7/2015²²...diffuse onset of erosions on the scalp, face, and chest.” FH Tr. 37-38; Pet. Ex. 4 at 23. At that visit he saw Dr. Pearson, another resident, and explained that the rash/lesions started with the scalp, nose, eye, and later, the remainder of the body. FH Tr. 37-38.

c. Petitioner’s Statement at the Entitlement Hearing

Petitioner attended the entitlement hearing, but he did not testify. However, at the conclusion of the hearing, he asked to be heard in response to some of the expert testimony during the hearing. He was permitted to do so.

Petitioner stated that, as a physician, he can give credible information about his health. Tr. 212. He stated that he took three tablets of lisinopril in 2009 for slightly elevated blood pressure but became dizzy when his blood pressure dropped too low, so he stopped taking it. He managed his blood pressure thereafter with diet and exercise. Tr. 212. He pointed out that his medical records do not reference lisinopril again until 2015, which was after he had “full-blown PV.” Tr. 212-13. He explained that in November 2015, his blood pressure became elevated from his pain, and he thought, “[t]hat’s all I need is another problem on top of the problem I have with PV.” He

²² The medical records reflect that the third HBV was administered on April 3, 2015—not in July 2015. Pet. Ex. 5 at 1. Petitioner testified that he likely told Dr. Pearson that he received the vaccine several months prior and only provided a generalization. FH Tr. 38-39.

took “one pill of lisinopril when [he] already had a full-blown PV.” Tr. 213. That night, he developed palatal swelling (angioedema), which is a dangerous complication and thought it best to have lisinopril entered into his medical record to be sure it was not given to him again inadvertently. Tr. 213. Thus, in his entire lifetime, he confirmed taking three lisinopril pills in 2009 and one in 2015. Tr. 213.

Dr. Henley agreed that diagnosing PV is difficult and, at the time, he attributed his gum bleeding to not flossing enough and found excuses for minor symptoms. He thought the skin lesions on his head were from the headlamp he wore during surgery. It never occurred to him that he had PV. Tr. 214. He had nose bleeds while seeing patients, another common symptom of PV. He treated with ophthalmology and dermatology until he said to the doctors, “[n]o more lotions and potions; take a biopsy. And at that point, we made a diagnosis.” Tr. 214.

Petitioner felt guilty for failing to make the diagnosis sooner, but Dr. Norris assured him he did a remarkable job because for many it can take two years before the diagnosis is made. Tr. 214-15. Petitioner added that due to the paucity of literature on PV, when a diagnosis is made two years later, most patients won’t remember any connection between a vaccine and the symptoms that are delayed and nebulous. Tr. 215.

Petitioner stated he did not take any other medications or lisinopril, does not smoke or drink, and has had a “fairly boring medical contributory background” with “the only major immunological insult [being] a triple vaccination.” Tr. 216-17.

d. Affidavit of Dr. John Blomstedt

In an affidavit dated December 5, 2016, Dr. Blomstedt affirmed that he worked with petitioner at RWMC in Scottsbluff, Nebraska and recalled petitioner asking him to look at a rash on his scalp he believed to be from his surgical lamp. Pet. Ex. 11 at 1. Dr. Blomstedt believed that was in June 2015. *Id.* Dr. Blomstedt affirmed performing a biopsy on petitioner in August 2015. *Id.*

e. Affidavit of Dr. Jim Massey

In an affidavit dated December 16, 2016, Dr. Massey affirmed that he worked with petitioner at RWMC. Pet. Ex. 12 at 1. Dr. Massey affirmed that approximately two years ago, petitioner asked him to look at an area on his shoulder that he was concerned about, as it previously had been cancerous. A biopsy was considered but never done and he could not recall why. *Id.*

E. Expert Opinions

a. Petitioner’s Experts

i. Dr. David Norris

1. Background and Qualifications

Dr. Norris received a Bachelor of Arts from Johns Hopkins and his medical degree from Duke University. Dr. Norris spent six months at Duke in cutaneous oncology and then went to Ohio State University to do his medical internship. He then went to the University of Colorado for

three years for a dermatology residency, where he has been since his residency concluded in 1977. He has been the Chairman of the Department of Dermatology for the last 21 years with his own focus on translational research to bring new treatments to his patients. His workload consists of patient care, teaching, and research. Tr. 66-67; *see also* Pet. Ex. 16.

Dr. Norris has practiced medicine for over 44 years and has treated patients with pemphigus vulgaris and other immunobullous diseases. Tr. 67. Since 1980, Dr. Norris has received funding from the National Institute of Health to focus on skin diseases, inflammatory skin diseases, and autoimmunity. For the last 18 years, he has received funding from the Veterans Administration to study mechanisms of melanoma. “So I know a fair amount about autoimmunity of the skin and cancer of the skin and immune responses in the skin.” Tr. 67.

Dr. Norris is also petitioner’s treating physician. Tr. 67. They are not social friends but share an interest in medicine and research. Tr. 81.

2. Opinion

Dr. Norris authored two reports. Pet. Ex. 15; Pet. Ex. 20.

Petitioner became Dr. Norris’s patient on September 24, 2015 after petitioner was diagnosed with PV, which was by then fully developed. Pet. Ex. 15 at 1; Pet. Ex. 4 at 1-13.

Dr. Norris summarized petitioner’s medical history noting no prior immunological disorders or history of drugs, alcohol, or smoking at the time petitioner’s PV was triggered. Pet. Ex. 15 at 1. Dr. Norris documented petitioner’s receipt of the first HBV vaccination on December 6, 2012. Blood work on September 4, 2014, showed an absence of anti Hep B titers and he received a second HBV vaccine on October 28, 2014, following which he developed some atypical lesion on his shoulder that resolved. *Id.* at 1-2; Pet. Ex. 1; Pet. Ex. 5. He received a third vaccination on April 3, 2015. Pet. Ex. 15 at 2; Pet. Ex. 5.

After the third vaccine, he developed skin lesions on his scalp thought to be from his headlamp, some scattered nose bleeds, bleeding gums, and an eye lesion. When the lesions progressed, he sought care from colleagues in dermatology, ophthalmology, and dentistry from June through August 2015. When the lesions failed to respond to treatment, petitioner insisted on biopsies which were performed on the scalp, nose, and eye lesions. The results were suggestive of acantholysis, meaning “... that the epithelium falls apart, the cells of the epithelium die, and an erosion or thin-roofed blister forms”, which is seen in pemphigus. Pet. Ex. 15 at 2. Blood tests were positive for anti-desmoglein antibodies. *Id.* Dr. Norris explained that PV is a life-threatening disease. Treatment involves steroids and IV immunotherapy which have significant risks of immunosuppression, placing the patient at risk for infection. Petitioner began intensive treatment in November 2015. *Id.* He suffered recurrent flares requiring IV infusions of Rituximab every 6 months and daily mycophenolate mofetil to control the autoantibody response that causes pemphigus. *Id.*; Pet. Ex. 20 at 1.

a. Prong I

Dr. Norris described PV as a rare and serious autoimmune disorder where circulating antibodies attack skin and mucous membranes creating open sores that multiply across the body and oral cavity. The disease is 70-95% fatal if not treated due to infections from the skin’s failure to protect. Pet. Ex. 15 at 1. PV is caused by antibodies directed against DSG 1 and 3 present in

the desmosomes resulting in the loss of cohesion between keratinocytes in the skin and disruption of the barrier which the skin provides. The process is classified as a Type II hypersensitivity reaction where antibodies bind to antigens on the body's own tissue. "The production of autoreactive antibodies to DSG1 and DSG3 is genetically determined by multiple genes" and the onset may be triggered by a variety of triggers such as stress, bacterial or viral infections, ultraviolet radiation, tissue trauma, and certain medications and chemicals. Pet. Ex. 15 at 2; Pet. Ex. 21.²³

Dr. Norris explained that the innate immune system recognizes specific molecular patterns of amino acids of pathogens—whether virus, bacteria, vaccine, or damaged tissue—and acts as the first line of defense with antibodies and T cells to defend against the pathogens. Pet. Ex. 20 at 1. The adaptive immune system recognizes the molecular tertiary structure of its targets. *Id.*

When a vaccine is injected, the innate immune system is rapidly activated and produces a range of pro-inflammatory cytokines such as tumor necrosis factor alpha ("TNF-alpha"), interleukin 6 ("IL-6"), and interleukin 1beta ("IL-1beta" or "IL-1b") within hours. Pet. Ex. 20 at 2. The cytokines activate macrophages and dendritic cells that enter tissue and further enhance a cytokine cascade, attracting T cells that further enhance the pro-inflammatory environment, producing tissue damage and the release of altered proteins. *Id.* The vaccine and host antigens travel to local and regional lymph nodes inducing local and systemic adaptive immunity. The T and B lymphocytes that are activated induce a complex immune response of both antigen-specific and non-specific cell populations. *Id.*

Dr. Norris continued, in pemphigus, autoantibodies against the self proteins DSG1 and 3 bond to the desmoglein surface of the keratinocytes inducing cell death, blister formation, and a complex cascade of tissue damage. Pet. Ex. 20 at 2. The mechanisms by which autoimmune diseases can be triggered include epitope spreading whereby damaged tissue produces "cryptotopes", which are themselves antigenic and activate B and T cells, producing more inflammation and further tissue damage; this process then activates immune cells programmed to react to other antigens, resulting in an autoimmune reaction. *Id.*; Tr. 68-69. Another viable mechanism is bystander activation, which occurs when there is an exaggerated immune response to an exogenous agent that induces local tissue inflammation and stimulation of otherwise unaffected normal cells which can result in the release of normally sequestered self-antigens. Pet. Ex. 20 at 3; Tr. 68-69. The inflammation may activate previously dormant auto-reactive Th-1 cells that then react against the newly released self-antigens. Bystander activation cannot be seen clinically, but it is a mechanistic component of the process that triggers pemphigus. Tr. 95. Friction, local bacterial infection, or ultraviolet radiation may participate in bystander activation that triggers PV disease. Pet. Ex. 20 at 3.²⁴

Dr. Norris detailed the "growing evidence" linking hepatitis B vaccination and pemphigus, citing case reports, charts in various studies, and clinical evidence like Dr. Henley's symptoms. Tr. 93. Citing *Berkun et al.*, Dr. Norris wrote that HBV vaccine is a well-known inducer of

²³ Anne Davidson, M.B., B.S. & Betty Diamond, M.D., *Advances in Immunology: Autoimmune Diseases*, 345 NEW ENG. J. MED. 340 (2001), filed as "Pet. Ex. 21" and "Pet. Ex. 29".

²⁴ All four experts agreed molecular mimicry is not a viable mechanism in this case. Therefore, any discussions regarding molecular mimicry by any of the experts will not be included herein.

autoimmunity and has been reported as triggering the emergence of PV as well as a wide variety of cutaneous reactions. Pet. Ex. 20 at 3; Pet. Ex. 15 at 2; Pet. Ex. 17 at 2²⁵ (“The associated vaccine most often involved with autoimmunity is the HBV vaccine, and its autoimmune side effects have been the subject of many studies in the last decade”. Table 1 contains autoimmune and skin disease after HBV vaccination including bullous pemphigoid.²⁶); Pet. Ex. 18;²⁷ Pet. Ex. 22.²⁸ *Berkun et al.* discussed the onset of PV in a patient following hepatitis B vaccine, suggesting that “in some cases vaccination may be the triggering factor for pemphigus in genetically predisposed individuals”. Pet. Ex. 17.²⁹ Dr. Norris acknowledged that *Berkun et al.* was a case report that showed only a temporal relationship between the onset of the patient’s pemphigus and the HBV vaccine and the authors did not discuss challenge-rechallenge. Tr. 72-73, 85-86; Pet. Ex. 17. Still, it showed that vaccines may be the trigger for pemphigus in genetically predisposed people. Pet. Ex. 17.

Dr. Norris referenced *Kridin et al.*, acknowledging that the study involved hepatitis B infection, not vaccination, but found an association between the infection and PV because “...many of the principal antigenic components of the hepatitis B virus are found in the vaccine and triggered by the vaccine...although it’s not a perfect comparison of those important antigens that can cause a reaction, this relates to some of them but not all of them, because it is vaccine versus virus.” Tr. 89; Pet. Ex. 18.³⁰

Dr. Norris also discussed *De Simone et al.*, which he acknowledged involved flu vaccine but showed that multiple environmental factors, such as ultraviolet radiation, trauma, drugs, and infections, can trigger autoimmune disease. Tr. 90; Pet. Ex. 19.³¹ In *De Simone et al.*, the flu vaccine was shown to exacerbate PV. Tr. 90. Dr. Norris submitted “...that a vaccination for a virus can do this is evidence [that a vaccine can trigger PV], although it’s not as good as if you had the hepatitis B [vaccine].” Tr. 91.

Dr. Norris stated, theoretically, any vaccine can induce PV or any autoimmune disease, although some vaccines are more likely to do so than others. Tr. 91. He cited *Nikkels et al.* in support of this view, stating that the article shows that some vaccines are more likely than others to cause reactions. Tr. 92. He acknowledged that *Nikkels et al.* did not include PV as a cutaneous adverse effect of either hepatitis A or B vaccines, but he maintained that PV is a very rare disease. Tr. 92; Pet. Ex. 22 at 7, Table V.³²

Genetic susceptibility to PV may be triggered by the immune activation capabilities of the HBV vaccine. Pet. Ex. 20 at 3. Literature supports PV’s association with various triggers including vaccines but a “really nice project on hepatitis B triggering pemphigus” does not exist. Tr. 93. There are only case studies reporting PV triggered by drugs and vaccines. Tr. 82-83. Dr. Norris explained that “...the absence of proof is not proof of absence...just because there is no study that

²⁵ Berkun et al., *supra* note 4.

²⁶ Dr. Norris explained that bullous pemphigoid and PV are both autoimmune blistering disorders in which autoantibodies bind to the skin, leading to blisters and serious disease. Tr. 74. Though bullous pemphigoid is more common and less deadly than PV, both can be triggered by hepatitis B vaccination. Tr. 74-75.

²⁷ Kridin et al., *supra* note 5.

²⁸ Arjen F. Nikkels et al., *Cutaneous Adverse Reactions Following Anti-Infective Vaccinations*, 6 AM. J. OF CLINICAL DERMATOLOGY 79 (2005), filed as “Pet. Ex. 22”, “Pet. Ex. 32”, and “Resp. Ex. C Tab 16”.

²⁹ Berkun et al., *supra* note 4.

³⁰ Kridin et al., *supra* note 5.

³¹ De Simone et al., *supra* note 6.

³² Nikkels et al., *supra* note 28.

has worked this out . . . doesn't mean that that isn't going on." Tr. 82-83. Dr. Norris agreed that there are no epidemiological studies that show HBV vaccine causes PV. Tr. 88-89. There are only case studies and clinical evidence as is seen here in petitioner, who got three challenges in the form of the HBV vaccine and got pemphigus with each challenge, thus providing "good clinical evidence". Tr. 94.

b. Prong II

Dr. Norris contends as an immunologic disease, PV may present with a few scattered lesions, then gradually spread to more extensive disease. Pet. Ex. 15 at 3; Pet. Ex. 21.³³ Here, petitioner received three HBV vaccinations with accelerating clinical disease following each one, reflecting "strong antibody responses to the hepatitis B virus". The third HBV vaccine on April 3, 2015 acted as the trigger for classic PV. The three vaccinations resulted in high levels of desmoglein antibodies, the underlying cause of skin lesions in PV, with high pathological levels exhibited on serum testing on September 16, 2015.³⁴ Tr. 69, 79-80, 88; Pet. Ex. 1 at 13; Pet. Ex. 15 at 3; Pet. Ex. 5 at 1. "His clinical progression to full blown PV is totally consistent with the Hepatitis B vaccinations being a trigger for PV." Pet. Ex. 15 at 3.

Further, the facts of this case provide strong proof of a rechallenge. Pet. Ex. 20 at 3. Dr. Norris explained that challenge rechallenge, wherein a patient is "challenged three times and they got the disease three times and each time it was worse", is strong clinical evidence of causation. Tr. 85. For example, if a medication is given with onset of disease that is mitigated when the medication is stopped but reappears when the medication is started again, then there is some evidence of causation. Tr. 86. If that is done three times with the same result, "then you really do have a case for causation." Tr. 86.

Dr. Norris agreed that while case reports provide only circumstantial information and temporal relationship, clinically, when temporal proximity occurs three times in a row with the same challenge, that can be evidence of causation. Tr. 84-85. He stated that temporal proximity alone may be evidence of causation depending on "how prominent the challenge and rechallenge is." Tr. 85. A temporal association becomes more significant in cases of challenge-rechallenge. Tr. 86. For example, if a new medication causes onset of disease that is mitigated when the medication is stopped, but returns when the medication is given again, evidence of causation begins. Tr. 86. "[I]f you do that three times, then you really do have a case for causation." Tr. 86. In practice no medical professional would give a medication following a reaction, much less three times. Tr. 86-87. This in part explains why there is not strong evidence of causation for either medications or vaccines for a particular disease. Tr. 87.

Here, petitioner had early signs of PV following the first HBV vaccine with bleeding gums and a rash that self-resolved. The second HBV vaccine was a rechallenge that resulted in a more profound rash, which also self-resolved. Tr. 80; Pet. Ex. 15 at 3. After the third vaccine, which marked the third "challenge", petitioner developed "a classic pemphigus picture with lesions that were very typical and [in] multiple places." Tr. 80; Pet. Ex. 15 at 3. As such, this was almost a

³³ Davidson & Diamond, *supra* note 23.

³⁴ While Dr. Norris stated in his report that this testing was done on July 26, 2017, the medical record he cited shows that petitioner's lab work showing high levels of DSG 1 and DSG 3 was performed on September 16, 2015. Pet. Ex. 1 at 13.

“textbook case report of challenge and rechallenge pattern of medication-induced autoimmunity.” Tr. 69, 78.

Dr. Norris stated that he also considered alternative triggers of petitioner’s PV, such as infection and medication. Tr. 78. Lisinopril could be a trigger but, unlike the vaccinations, it was not taken three times with increasing disease response with each challenge. Tr. 79.

Dr. Norris stated that he started treating petitioner after he had a “pretty clear” diagnosis of PV. His unusual history made the HBV vaccinations the logical trigger for his PV from a clinician’s view. Tr. 70. Dr. Norris conceded that petitioner was the only patient he has seen with an apparent vaccine-triggered PV, but then PV is a very rare disease. Tr. 73. He stated that when there are autoimmune diseases of the skin, clinicians look for triggers that “turn on the disease”. Tr. 70. He teaches his residents that autoimmunity requires “genetics, susceptibility, and then . . . immunologic triggers that alter the defenses against developing tolerance and that stimulate those inflammatory processes that can lead to autoimmunity.” Tr. 70. The HBV vaccine was a “component” of petitioner’s development of PV because it “turned on the immune response to attack a self-antigen”—an induced autoimmunity—which is a process that requires a “genetic predisposition, trigger, and then dysfunction of the normal controls that prevent the production of autoantibodies or autoreactive T cells.” Tr. 77-78. Here, the HBV vaccine was the trigger or “critical component” in petitioner’s development of PV, which required three challenges before the clinical disease clearly manifested. Tr. 78.

c. Prong III

Dr. Norris contended that a PV flare can occur as early as one week after vaccination in patients with existing disease. Pet. Ex. 15 at 3. How long it takes after a single vaccination or multiple serial vaccinations to trigger the development of PV is not established. *Id.* However, he testified that the onset of petitioner’s PV thirty days after receipt of the third vaccine is medically reasonable. Tr. 71-72. “The pattern of Hepatitis B vaccination triggering PV reported in the literature suggests that multiple serial hepatitis B vaccinations can induce PV in classic immunization and booster manner, i.e. the development of pathogenic autoantibodies in PV after multiple serial vaccinations induce sufficient anti-DSG antibodies to induce the disease PV.” Pet. Ex. 15 at 3.

Dr. Norris agreed that case reports provide only circumstantial information and show a temporal relationship, which is not the same as causation; however, he argued that clinically, when temporal proximity occurs three times in a row, with the same three challenges, that can be evidence of causation. Tr. 84. Whether temporal proximity alone proves causation “... depends how prominent the challenge and rechallenge is.” Tr. 85. Dr. Norris opined that this was a clear case of challenge-rechallenge. Tr. 69, 78.

ii. Dr. Vera Byers

1. Background and Qualifications

Dr. Byers received a bachelor’s degree in bacteriology then a Ph.D. in immunology; she did post-doctoral work in immunology, a residency in internal medicine, and a post-doctorate fellowship in cancer and cancer immunotherapy in clinical immunology, and she served as a consultant in orthopedic oncology in osteogenic sarcoma. Tr. at 6-7. More than half of her current

work is expert work, including in the Vaccine Program and in cases involving environmental exposures to toxic chemicals. Tr. 52. She confirmed that she has not maintained a clinical practice for roughly 20 years, and she no longer has admitting privileges, teaches, or holds any research positions. Tr. 52-53. She is a consultant in immunology at a private corporation. Tr. 53-54. She is board-eligible in allergy and immunology but never took the test to become board-certified. Tr. 54. She has not written any papers on pemphigus vulgaris. Tr. 56. Her papers are about causes of autoimmune diseases in general. Tr. 56. She has not published on hepatitis B vaccine. Tr. 56-57. Dr. Byers has done research in drug development and immunology over the years. Tr. 7-8. She has done research on vaccines her whole career. Her Ph.D. thesis was in vaccines, looking at how you break tolerance. Tr. 8. In or around 1971, she worked for NIH on immunologic and cancer drugs. Tr. 8.

2. Opinion

Dr. Byers noted that, other than having hepatitis as a child, petitioner's medical records were unremarkable. Pet. Ex. 23 at 2. His work required him to take the HBV vaccination when he was found to be without anti-hepatitis B antibodies. Following the first Hep B vaccine, he still lacked anti-HBV antibodies and received second and third vaccinations. *Id.*

Dr. Byers provided a history of events following petitioner's receipt of the three HBV vaccines which included: he had a chest rash shortly after the December 6, 2012 vaccine that resolved on its own; heavy dental bleeding on February 19, 2013; gum inflammation on August 6, 2014; still anti-hepatitis antibody negative on September 4, 2014. Pet. Ex. 23 at 2. Following the second vaccination on October 28, 2014, he developed a rash on his chest and lesion on his shoulder that resolved within weeks. *Id.* After a third vaccination on April 3, 2015, he had a stye that appeared on April 14, 2015; anti-hepatitis antibody positive on May 15, 2015; bleeding gums and lesions on his scalp and eyelid on June 23, 2015; an abscessed tooth on June 28, 2015; and a clogged gland in his right eye on August 17, 2015. Biopsies of the scalp and nose lesions were positive for PV on August 24, 2015; a biopsy of his right eyelid was positive for PV on August 27, 2015. Elevated levels of DSG 1 and 3 were documented on September 16, 2015. *Id.*

Dr. Byers agreed with Dr. Norris's opinions and his description of PV and that early signs of PV may have been seen following the first and second vaccinations in a classic pattern of epitope spreading, leading to increasingly extensive disease. Pet. Ex. 23 at 3.

Dr. Byers disagreed that lisinopril was a more likely cause of petitioner's PV since the medical records do not provide when the medication was taken. Pet. Ex. 23 at 3. Further, she disagreed that the literature lacked support for a cross reaction between antigens in the HBV vaccination and DSG1 and 3. *Id.* at 3, 5. Finally, she disagreed that petitioner's advanced dental disease on February 19, 2013 could have been the trigger of his PV, explaining that this idea "doesn't fit with the medical history, which shows a slow progression from almost asymptomatic disease" to positive biopsies for PV and high levels of anti-DSG. *Id.* at 4.

a. Prong I

Dr. Byers described PV as a rare autoimmune disease involving antibodies against two proteins—DSG 1 and 3. Tr. 9. Many autoimmune diseases, including PV, have a strong genetic

component. Tr. 18-19. There are also environmental triggers, including vaccines, that can induce autoimmune disease. Tr. 10-11.

According to Dr. Byers, the hepatitis B vaccine is “one of the more common” environmental triggers of autoimmunity. Tr. 11. The body contains autoreactive B and T cells that are usually quiescent but can react to various distal antigens later in life. Tr. 11, 18-19. These B cells are very sensitive to proinflammatory cytokines produced by vaccination which is critical to the effectiveness of the vaccines. Pet. Ex. 23 at 5. The HBV³⁵ vaccine produces a very strong immune response that generates proinflammatory cytokines, such as IL-6 and tumor necrosis factor, that can activate the autoreactive B and T cells to become dysregulated and reactive against DSG 1 and 3. Tr. 11-12, 17-19; Pet. Ex. 23 at 5. If DSG proteins are destroyed, blisters result because the epidermis cannot bind properly. Tr. 9, 11-12, 18-19.

Dr. Byers explained the process of epitope spreading as producing cytokines that can trigger the destruction of proteins like DSG, in addition to neoantigens that are immunogenic on their own. Tr. 17. As epitope spreading progresses, there is an increasing number of immunocytes that are directed against various antigens, even distal antigens. Tr. 18. Epitope spreading involves focal tissue damage produced by some other mechanism that results in cryptotopes presented to the immune system by damaged cells and spreads, causing an autoimmune mechanism. Pet. Ex. 23 at 4. Bystander activation is more localized and involves increasing reactivity of local immune cells that may react against other cells. Tr. 18. She stated that data supports HBV vaccine as an inducer of autoimmune disease by bystander activation. Tr. 61.

Dr. Byers also described the process of challenge-rechallenge, which she defined as a reaction elicited by one dose of a drug which is reproduced by the next dose. Pet. Ex. 23 at 5. When a patient has a very similar reaction after a second exposure, that lends weight to the exposure being the etiology of the problem. Tr. 20. The term “challenge-rechallenge” is used in the Vaccine Program to include worsening symptoms after the rechallenge. Pet. Ex. 23 at 5. Dr. Byers explained that invoking already present memory B cells which react with autologous antigens and are controlled by regulatory T cells usually occurs without event. *Id.* However, memory B cells are very sensitive to proinflammatory cytokines produced by vaccines which is critical to their effectiveness. Foreign antigens produce cytokines, and vaccines that contain adjuvants make the production of cytokines even more vigorous. *Id.*

Like Dr. Norris, Dr. Byers cited to *Kridin et al.* as a large-scale epidemiological study that found those with pemphigus have a statistically higher prevalence of HBV infection when compared to controls. Tr. 12-13; Pet. Ex. 18;³⁶ Pet. Ex. 23 at 3, 4. Acknowledging that the study involved chronic Hepatitis B infection not HBV vaccination, she explained that “when a vaccine is considered a suspect in an *autoimmune* disease, it is usually agreed that information of autoimmune diseases which occur with the active disease can be used to support an association, because the important epitopes on the vaccine are the same as those on the infective disease.” Pet. Ex. 23 at 4 (emphasis in original); Tr. 57, 62-63. Dr. Byers responded to Dr. Levinson’s criticism of *Kridin et al.*, stating that the study included 1,985 patients with PV and 9,874 controls, and the results were statistically significant. Pet. Ex. 23 at 3, 4; Tr. 21-22, 49, 57.

³⁵ The transcript incorrectly reads HPV rather than HBV in some places.

³⁶ Kridin et al., *supra* note 5.

Dr. Byers pointed to Table I in *Berkun et al.*, which contained a list of autoimmune diseases associated with HBV vaccine and included bullous pemphigoid, which she stated refers to PV. Tr. 14-15, 50-51; Pet. Ex. 17 at 2.³⁷ Dr. Byers agreed that case reports report temporality and can be purely coincidental, but even with other differential diagnoses reported, the various authors from the articles contained in Table I felt that the PV was associated with the HBV vaccine. Tr. 50-51; Pet. Ex. 17.

Dr. Byers discussed *Tavakolpour* to show that influenza, HBV, anti-rabies, and tetanus vaccines have all been linked to the development of PV. Tr. 22; 25-26; Resp. Ex. C Tab 12 at 7, Figure 1.³⁸ She added that *Tavakolpour* concluded, “Infections stimulate various immune responses (usually Th1 and Th17 associated responses) . . . autoinflammatory diseases induce vigorous immune responses as well as dysfunction of regulatory responses. The promotions of humoral (antibodies) and cellular immune responses are undeniable outcomes of any vaccines, which contribute to the progression of pemphigus.” Tr. 26-28; Resp. Ex. C Tab 12 at 7-8. Dr. Byers conceded at hearing that the article included over 150 citations that she did not review. Tr. 64.

b. Prong II

Dr. Byers explained that many autoimmune diseases including pemphigus have a strong genetic component. Tr. 18-19. Petitioner is an Ashkenazi Jew, and thus carries a higher degree of pemphigus;³⁹ either from birth or during development, he developed certain B cells and possibly T cells that were specific for desmoglein. The HBV vaccine triggered an “intense” inflammatory process that generated cytokines, which in turn began the disease process. Tr. 19.

Dr. Byers further opined that the course of events in this case fits with a challenge-rechallenge with dental bleeding and inflammation 1.5 months and 8 months after the first vaccination that then calmed. After the second vaccination on October 28, 2014, petitioner developed a rash on his chest and a lesion on the right shoulder. The disease then calmed again, indicative of low-level activation of autoreactive T cells consistent with bystander activation. Pet. Ex. 23 at 5-6. Then after the third vaccination, he developed bleeding gums, as well as lesions on the scalp and eyelid then nose, with biopsies positive for PV and ultimately DSG 1 and 3. *Id.* at 5. The “burst of activity” following the third vaccination left petitioner disabled. *Id.* at 5-6. She classified the second and third HBV vaccinations as rechallenges. *Id.* at 5.

Dr. Byers clarified that she initially opined that the second HBV vaccine activated the immune system against DSM through epitope spreading. Tr. 19-20, 29, 58-59. However, she stated at hearing that she now believes the first injection petitioner received triggered the start of petitioner’s PV, with the first symptom being heavy dental bleeding in February 2013. Tr. 29, 58-60. The second HBV vaccine resulted in a rash on his shoulder and chest, which she explained was consistent with the progression of pemphigus. Tr. 21. Then, after the third vaccine, there were

³⁷ Berkun et al., *supra* note 4.

³⁸ Soheil Tavakolpour, *Pemphigus Trigger Factors: Special Focus on Pemphigus Vulgaris and Pemphigus Foliaceus*, 310 ARCHIVES OF DERMATOLOGICAL RES. 95 (2018), filed as “Resp. Ex. C Tab 12”.

³⁹ Kridin et al., *supra* note 5.

similar lesions that progressed to bleeding gums, a tooth abscess, and lesions on the eyelid and scalp with a biopsy positive for pemphigus in August 2015. Tr. 21, 58-59. Therefore, it was her opinion that the initial two vaccines increased the “pool of B cells” and likely also T cells, which were ultimately triggered by the third vaccination. His history represents a challenge-rechallenge. Tr. 29-31.

Dr. Byers referred to petitioner being hepatitis B antibody negative in September 2014 after the first vaccine, but he later tested positive for antibodies after the third vaccine. Pet. Ex. 1 at 9. However, DSM 1 and 3 levels were not measured until September 16, 2015, at which time they were elevated. Tr. 29-30, 33-38; Pet. Ex. 1 at 1, 9, 13.

Dr. Byers disagreed that lisinopril was the likely cause of petitioner’s PV because it is not known when petitioner started taking lisinopril, and there is no evidence that lisinopril can cause PV. Pet. Ex. 23 at 4. She further disagreed that petitioner’s gum disease in February 2013 caused and/or initiated petitioner’s PV by epitope spreading, given the slow onset of petitioner’s PV. However, Dr. Byers noted that the dental bleeding in February 2013 could have started the autoimmune process, with the subsequent vaccinations resulting in epitope spreading. *Id.* at 5.

Summarily, she concluded that the most probable series of events included bystander activation of a small pool of mature autoreactive B cells from petitioner’s first HBV vaccine, followed by re-challenge and epitope spreading with resultant symptoms becoming more widespread. Following petitioner’s third HBV vaccine, “[t]he autoreactive B cells are mature and would be expected to begin producing antibod[ies] within four weeks after stimulation and continue to accumulate until they could no longer be controlled.” *Id.* at 6.

c. Prong III

Dr. Byers stated that the “most obvious onset of the PV” was when petitioner developed a stye, then lesions and bleeding gums in the weeks after the April 3, 2015 HBV vaccine. Pet. Ex. 23 at 5. The tempo of his PV accelerated after the April 3, 2015 vaccination, which all the experts agree occurred. *Id.*

b. Respondent’s Experts

i. Dr. Arnold Levinson

1. Background and Qualifications

Dr. Levinson obtained his medical degree from the University of Maryland in 1969. Tr. 168. He did his residency in internal medicine, a one-year fellowship in immunology at the University of Pennsylvania (“UPenn”), then went to San Francisco for a year for clinical immunology research, then returned to UPenn for two years for a fellowship in allergy and clinical immunology. Tr. 168-69. He left to do his “armed service duty” and was appointed to a position at Walter Reed Army Medical Center (“Walter Reed”) where he spent three years running a clinical and translational immunology research program and seeing patients with allergy and clinical immunology types of diseases. He then took a yearlong sabbatical at the University of

Oxford in England in molecular biology. Tr. 169. Following Walter Reed, he returned to UPenn and joined the faculty of the allergy and immunology division of the department of medicine. Tr. 170.

Dr. Levinson described his expertise as allergic disorders—asthma, sinusitis, rhinitis, urticaria—and extends to complex hypersensitivity disorders involving any number of immunologic cells that fight infections and complex autoimmune diseases. Tr. 170. He is board certified in internal medicine, allergy, and immunology. Tr. 170. While at UPenn, he researched the activation and regulation of T cells and B cells. Tr. 172. His research interests were in the structure and functional relationships of antibodies, what activated B cells, and the process of how B cells differentiated into antibody secreting cells, which included physiologic kinds of antibodies. He also studied the interaction between the innate and adaptive immune systems. Tr. 172. Further, his interests included hypersensitivity to injected and oral products like drugs and biologic immune modifiers. Tr. 172-73. He spent most of his professional life trying to understand the pathogenesis of a prototypic autoantibody-mediated disease called myasthenia gravis, which is neurological and caused by the action of IgG autoantibodies, as is PV. Tr. 173. He has served on journals, published, lectured, and received awards in his field. Tr. 173-77; *see also* Resp. Ex. B. He was recognized as an expert in immunology. Tr. 178.

2. Opinion

Dr. Levinson issued three reports in this case after review of the evidence filed and his own research. Resp. Ex. A; Resp. Ex. F; Resp. Ex. H.

Dr. Levinson's summary of petitioner's medical history included a drug allergy to lisinopril, to which he developed angioedema, and penicillin⁴⁰ at the age of 9 post-appendectomy, which caused hepatitis. Resp. Ex. A at 2.

Dr. Levinson agreed that petitioner has PV. Resp. Ex. A at 3. He further agreed with Dr. Norris's description that PV is an intraepidermal blistering mucocutaneous autoimmune disease caused by IgG antibodies directed against desmogleins and that it is a deadly disease if left untreated. *Id.* at 3-4. It is Dr. Levinson's opinion, however, that the HBV vaccine did not play a role in petitioner's development of PV. Tr. 179.

a. Prong I

Dr. Levinson argued that while Dr. Norris described the important pathogenic role of anti-desmoglein antibodies in PV, he failed to describe how HBV vaccine is linked to this mechanism or how any immunological challenge might lead to the onset of the disease. Resp. Ex. A at 5; Resp. Ex. F at 1. "[T]here has long been conjecture about immunologic challenges with agents like bacteria and viruses causing [PV], there is no reliable evidence...that hepatitis B vaccination causes this disease." Resp. Ex. A at 5. The literature relied on by Dr. Norris "fall[s] significantly short of providing evidence for such a causal link between hepatitis B infection or hepatitis B

⁴⁰ Petitioner testified to having contracted hepatitis as a child in Poland from a reused needle used to administer penicillin—not the penicillin itself. FH Tr. 42-43.

vaccination and PV.” *Id.*; Resp. Ex. F at 2. In his opinion, Dr. Norris’s arguments were mere conjecture. Resp. Ex. F at 1-2.

Critiquing the literature petitioner’s experts relied on, Dr. Levinson stated that *Berkun et al.* is a case report with a lapse of three months between vaccination and the onset of PV symptoms, “[e]ven the authors indicated that the association may have been nothing more than a coincidence.” Resp. Ex. A at 5; Resp. Ex. C Tab 1 at 2.⁴¹ An antibody-mediated mechanism would be expected to manifest clinically within a few days or weeks of vaccination, depending on whether it was primary or a booster immune response. Resp. Ex. A at 5. Although causality was not demonstrated in *Berkun et al.*, Dr. Norris relied on it in formulating his causality opinion. *Id.*

Dr. Levinson also took issue with Dr. Byers’s reliance on *Kridin et al.*, pointing out that it discussed PV in persons with chronic HBV infection not HBV vaccination. Resp. Ex. A at 5; Resp. Ex. C Tab 2;⁴² *see also* Resp. Ex. H at 1; Tr. 185-86. Dr. Levinson explained that the vaccine contains the surface antigen, which is only one protein of the HBV virus, while the wild type virus expresses “a myriad of antigenic epitopes, determinants, antigens...not expressed in the vaccine.” Tr. 188. The immune response to a virus is “incredibly more intense . . . and much greater in terms of the various components of the immune system” than the immune response to a vaccine. Tr. 188-89.

Further, in his opinion, *Kridin et al.* only “reported a minor statistical association between chronic hepatitis B infection and pemphigus vulgaris.” Resp. Ex. A at 5. The authors added that the temporal order of appearance of PV and HBV infection in the patients studied was lacking, making it impossible to analyze causality. *Id.* They further stated that it is possible that those with PV are at risk for developing chronic HBV infection due to the immunosuppressants used to treat PV, rather than the other way around. *Id.*

Dr. Levinson disagreed that if an infection can cause the development of autoimmune disease, a vaccine “administered to protect against infection...poses a risk for causing the same autoimmune disease.” Resp. Ex. H at 2. He explained that “the final common pathway in an autoimmune disease is attack of the body by a host system”, but the virus itself also causes significant damage; without that serious damage from the virus, the immune system would likely not react against itself. Tr. 204-05. He concurred with Dr. Simpson that the impact of HBV infection and HBV vaccination in the host is not equivalent. He further argued that no reliable evidence exists that even an HBV infection can cause PV. Resp. Ex. H at 2.

Dr. Levinson argued that Dr. Byers’s opinion—that petitioner had a population of autoreactive PV-specific memory B cells that were activated to differentiate into anti-DSG antibody secreting cells as a result of the HBV vaccinations—was speculative. Resp. Ex. H at 2. He also referred to Dr. Norris’s opinion as “built on a house of cards.” Resp. Ex. A at 5.

Dr. Levinson explained the process of bystander activation as autoreactive T cells and B cells being activated independently of exposure to their autoantigen. Resp. Ex. H at 2-3; Tr. 189-90. Because T and B cells are activated despite not seeing their own specific antigen, they are

⁴¹ Berkun et al., *supra* note 4.

⁴² Kridin et al., *supra* note 5.

referred to as “bystanders”. Tr. 191. However, while bystander activation has been “demonstrated following active infection with a number of microbes”, it has not been demonstrated to be induced by vaccination. Resp. Ex. H at 3; Tr. 189-93. There is no reliable evidence to suggest that “bystander immunologic cross-talk ever leads to the development of autoimmune disease in otherwise healthy hosts following vaccination.” Resp. Ex. H at 3; Tr. 201, 203. If bystander activation of autoreactive T cells were important, flares of disease activity would be seen in patients with known autoreactive T and B cells (like multiple sclerosis, lupus, or rheumatoid arthritis). However, this is not the case in medical/scientific literature. *Id.*; Resp. Ex. H Tab 1;⁴³ Resp. Ex. H Tab 2.⁴⁴ Dr. Levinson did not know if vaccines can cause epitope spreading because where vaccines have been shown to be causally involved in the development of autoimmune disease, epitope spreading was not being investigated. Tr. 202.

According to Dr. Levinson, pro-inflammatory cytokines produced in the local lymph nodes draining from the injection site in humans “represents a physiological innate immune response that is necessary to promote the induction of a protective vaccine antigen-specific adaptive immune response.” Resp. Ex. H at 3.

Initially, when asked if HBV vaccine can trigger and/or cause other autoimmune diseases, Dr. Levinson took issue with the word “cause”, stating that “[a]nything can possibly do something, but is it likely...no. Not at all.” Tr. 196. Later, he stated that based on the literature, it is his opinion that vaccines “do not cause bystander activation that leads to an autoimmune response.” Tr. 201. Dr. Levinson clarified that vaccines clearly cause some autoimmune responses; however, he maintained that “it ain’t hepatitis B vaccine, and it’s not pemphigus vulgaris.” Tr. 202. He stated that he is not aware of HBV vaccine acting as a trigger for any autoimmune disease, including PV. Tr. 183, 186-87, 197-98.

Dr. Levinson responded with a “resounding no” when asked if the TNF alpha produced by the body during an immune challenge is the same regardless of the challenge. Tr. 205. He explained that “the whole immune response is totally qualitatively different when you’re dealing with a viral infection than when you’re . . . dealing with a vaccine.” Tr. 206. However, he then conceded that the biochemistry—the molecular molecule of the TNF alpha—is the same, but the quantity is different. Tr. 206-07. When pressed on whether cytokines are the same regardless of trigger, Dr. Levinson responded, “You definitely didn’t hear that.” Nevertheless, when asked again whether “IL-1 is IL-1”, regardless of what’s producing it, Dr. Levinson stated that “IL-1 biochemically—we compare IL-1 in my big toe to IL-1 in my left ear, that’s IL-1,” but that is entirely irrelevant. Tr. 207-08.

When asked what it would take for him to agree there as an association between a vaccine and PV, he stated, although PV is rare, it would take “a lot more than a single case report of a vaccine that’s given to millions . . . around the world.” Tr. 198, 200. He added that he would need a “biologically plausible mechanism that is consistent with what [is understood] to be important in the development of autoimmunity”, which was not presented in this case. Tr. 198-200.

⁴³ Yovana Pacheco et al., *Bystander Activation and Autoimmunity*, 103 J. OF AUTOIMMUNITY 102301 (2019), filed as “Resp. Ex. H Tab 1”.

⁴⁴ Johanna Westra et al., *Vaccination of Patients with Autoimmune Inflammatory Rheumatic Diseases*, 11 NATURE REVIEWS RHEUMATOLOGY 135 (2015), filed as “Resp. Ex. H Tab 2”.

Dr. Levinson was asked about the *Ong et al.* case report discussing lisinopril and pemphigus, which states that “[t]he maximum latency to development of pemphigus reported for ACE inhibitors is 2 years with the average being close to 6-12 months.” Tr. 193-95; Resp. Ex. A Tab 2 at 4.⁴⁵ Dr. Levinson stated he did not find this statement to be particularly significant because a lot can happen in two years after the administration of a drug or vaccine. Tr. 194-95.

b. Prong II

Dr. Levinson agreed that challenge-rechallenge is “an important consideration” in immunology. Tr. 209. However, he disagreed with how petitioner’s experts described the progression of his symptoms. He had a mild ephemeral skin reaction after the first vaccine, then a few months later had gum bleeding and gum inflammation. Tr. 181. After the second vaccine, petitioner developed an ephemeral skin rash on his chest and a lesion on his shoulder that lasted about two weeks. Tr. 181-82. Dr. Levinson did not “see that chronology of events as being consistent with progressive disease development following the two vaccinations.” Tr. 182.

Dr. Levinson acknowledged that petitioner had high levels of DSG antibodies on serum testing after his third HBV vaccination. Resp. Ex. A at 3, 5; Pet. Ex. 1 at 13. However, he disagreed that petitioner’s PV was related to the three HBV vaccines, referring to that opinion as “nothing more than conjecture.” Resp. Ex. A at 5. Dr. Levinson stated no evidence existed that any of the vaccinations resulted in high levels of anti-DSG antibodies because no testing was done until 3 and half months⁴⁶ after the third vaccination. *Id.* Additionally, no mechanistic theory was provided for how the three vaccinations gave rise to high titers of anti-DSG antibodies. *Id.* at 5-6. Further, petitioner failed to show any anti-Hep B antibodies on tests conducted after the first two HBV vaccinations. *Id.* at 6. Dr. Norris did not explain how petitioner could manifest signs of early anti-DSG antibody-mediated damage to his skin if his immune system “failed to respond to the allegedly provocative hepatitis B virus antigens” in the first two HBV vaccines.⁴⁷ *Id.*; Resp. Ex. H at 3; Tr. 182.

Dr. Levinson argued that pemphigus is associated with a number of “drugs” including non-sulfhydryl drugs, such as lisinopril. Resp. Ex. A at 4. Petitioner was prescribed lisinopril and had a reaction of angioedema, defined as swelling in the skin or mucosa “perhaps lining the oral cavity or the gastrointestinal tract.” Tr. 180. Dr. Levinson argued that ACE inhibitors have been “definitely associated with the development of PV, unlike hepatitis B vaccine”. Tr. 180. He explained that “the average incubation period between the start of the offending non-sulfhydryl ACE-inhibitor and the average onset of [PV] was 128 days”, which is a little over 4 months. Resp. Ex. A at 4. He believed it was important to consider this drug as a potential alternative explanation for petitioner’s development of PV. Tr. 180-81. Dr. Levinson argued that Dr. Byers dismissed

⁴⁵ Colin S. Ong et al., *Drug-Related Pemphigus and Angiotensin Converting Enzyme Inhibitors*, 41 AUSTRALIAN J. OF DERMATOLOGY 242 (2000), filed as “Resp. Ex. A Tab 2”.

⁴⁶ Petitioner’s labs showing high levels of anti-DSG 1 and 3 were performed on September 16, 2015—approximately five and a half months after the third vaccination on April 3, 2015. Pet. Ex. 1 at 13.

⁴⁷ Petitioner failed to show antibodies to Hep B on September 4, 2014 after the first vaccination, prompting the second and third vaccines. It is unknown whether he had antibodies after the second HBV vaccine because he was not tested. Pet. Ex. 1 at 1.

lisinopril as a causal factor in this case, but she did not rule out that lisinopril was as viable a PV-causing candidate as the HBV vaccination. Resp. Ex. H at 2.

Dr. Levinson was asked if a patient presented to him reporting a rash on his chest following a viral infection which was later diagnosed as PV would he think the viral infection caused the PV? He responded that he would not and would only say it was a possibility just like lisinopril is a possibility. Tr. 200-01. He was then asked if he had a patient who received the hepatitis B vaccine three times and PV was triggered after each exposure, if he would expose his patient to another vaccine or would the vaccine be contraindicated? Tr. 208. Dr. Levinson stated, “[s]ame answer as Dr. Simpson gave you. I will not respond to a hypothetical question.” Tr. 208. Counsel noted that Dr. Simpson had deferred to him as the immunologist. Tr. 208. I instructed Dr. Levinson to answer the question as best as he was able. Tr. 208-09. Nevertheless, Dr. Levinson refused to answer. Tr. 209.

Finally, Dr. Levinson was asked whether he would withhold a medication in a patient who previously had an adverse immunological response to that medication several times. Dr. Levinson stated he would have to have a very clear medical history, decide the risk versus benefit of taking the drug, and consider alternative ways to administer the drug. Tr. 209-10. He conceded he would also consider not giving that patient the drug again. Tr. 210.

In conclusion, Dr. Levinson opined that there is no evidence supporting a causal relationship between petitioner’s April 3, 2015 HBV vaccination and his development of PV. Tr. 193.

c. Prong III

Dr. Levinson opined that since it has not been established that HBV vaccine or any vaccine can cause PV, addressing how long it would take for onset after one or multiple vaccines is “sheer folly”. Resp. Ex. A at 6. He stated “... there is absolutely no reliable data in the literature that indicates that hepatitis B vaccine induces de novo pemphigus vulgaris or exacerbates preexistent pemphigus vulgaris. So, it is surely a stretch to make any reliable prognostications about the time it would take to develop these outcomes since they don’t seem to occur.” *Id.* at 7.

ii. Dr. Cory Simpson

1. Background and Qualifications

Dr. Simpson received his Ph.D. then his medical degree from Northwestern University with a focus on biomedical research. Resp. Ex. I; Tr. 99. His research was primarily on keratinocytes, which are the main cells that comprise the outer layers of the skin. Tr. 99-100. His Ph.D. was “specifically focused on the function of” DSG 1. Tr. 100. He then completed a medical internship in internal medicine at the University of Chicago then a three-year residency at the University of Pennsylvania in dermatology. Tr. 101. He trained under Dr. Masayuki Amagai at Keio University in Tokyo, Japan, who discovered that DSGs were the target antigens in pemphigus. Tr. 102. Dr. Simpson now spends the majority of his time in a laboratory, conducting research on the epidermis and skin disease. Tr. 103. His research is funded by NIH. Tr. 103. He has been on faculty at both UPenn and the University of Washington. Resp. Ex. I; Tr. 103.

2. Opinion

Dr. Simpson agreed that petitioner has PV, a rare autoimmune disease caused by aberrant production of auto reactive antibodies that bind to and compromise the integrity of the skin and mucous membranes. Resp. Ex. C at 3. In Dr. Simpson's opinion there is no reliable evidence linking HBV vaccine to PV and the theory in this case is not accepted or taught in the dermatologic community. According to Dr. Simpson, the exact pathogenesis of PV is not understood and there is no large scale unbiased clinical data directly assessing whether a statistically significant relationship exists between HBV vaccine and PV, therefore, one cannot state that it is more likely than not that the HBV vaccine directly caused petitioner's PV. Resp. Ex. C at 7-8.

a. Prong I

Dr. Simpson described PV as an autoimmune disease, meaning the body attacks itself when it recognizes specific proteins as foreign and starts making antibodies against them. Tr. 112. Dr. Simpson submitted that PV is proximally caused by pathogenic autoantibodies that recognize, bind to, and impair the function of DSG 1 and 3, which are essential for holding together the cells that make up the skin and mucous membranes. This causes the tissues to fall apart, leading to the blisters and lesions seen on PV patients. Tr. 112; Resp. Ex. C at 4. He described it as a painful and terrible disease. Tr.112-13. However, what initiates the production of autoantibodies or why certain individuals develop PV is not understood. Tr. 113; Resp. Ex. C at 4. Dr. Simpson agreed that the point of vaccines is to produce protective antibodies. Tr. 152.

He submitted that none of the immunological mechanisms that can lead to autoimmunity—molecular mimicry, bystander activation, or epitope spreading—have been studied in the context of PV and HBV vaccine. Resp. Ex. E at 1. He argued that no reliable evidence exists linking HBV vaccine to PV or autoimmune disease and the link proposed in this case has not been tested using large scale, case control studies required for establishing a “robust and unbiased correlation between a disease and potential risk factors”. But even a case control study cannot imply that any examined exposure directly caused a disease. Resp. Ex. C at 4, 7; Resp. Ex. E at 1; Resp. Ex. E Tab 1;⁴⁸ Resp. Ex. G at 1. The leading textbooks do not mention any vaccines as causative in the pathogenesis of pemphigus. Tr. 153; Resp. Ex. C at 4; Resp. Ex. C Tab 5;⁴⁹ Resp. Ex. C Tab 6.⁵⁰ He further stated that, despite training at UPenn under three of the world's experts on PV, conducting multiple literature searches, and attending annual dermatology meetings, he has not encountered “any reliable research” naming the HBV vaccine as a cause of PV. Tr. 125-26, 130-31.

Dr. Simpson explained that the best evidence is large-scale meta-analyses combining the results of multiple clinical studies and case studies are “merely observations...that are hypothesis-

⁴⁸ J. Mark Elwood & Rohan Ameratunga, *Autoimmune Diseases After Hepatitis B Immunization in Adults: Literature Review and Meta-Analysis, with Reference to 'Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants' (ASIA)*, 36 VACCINE 5796 (2018), filed as “Resp. Ex. E Tab 1”.

⁴⁹ William D. James M.D. et al., *Chronic Blistering Dermatoses*, in ANDREWS' DISEASES OF THE SKIN 451 (2016), filed as “Resp. Ex. C Tab 5”.

⁵⁰ Masayuki Amagai, *Pemphigus*, in DERMATOLOGY 494 (2018), filed as “Resp. Ex. C Tab 6”.

generating rather than hypothesis-testing.” Resp. Ex. C at 7; Tr. 132, 153-54. “Since the pathogenesis of pemphigus is still under investigation and has not been robustly linked in a large-scale study to any particular exogenous factor, it is without solid scientific rationale to assert a causative link between the HBV vaccine and pemphigus based on a single published case report as has been alleged by Dr. Norris.” Resp. Ex. C at 7. Dr. Simpson further disagreed that the HBV vaccine is a well-known inducer of autoimmunity. Resp. Ex. E at 1.

Dr. Simpson’s comprehensive literature search on pemphigus and other vaccines revealed only individual case reports of PV following Typhoid booster; rabies vaccination; anthrax vaccine; and a large cohort study of 242,720 women vaccinated against Human Papilloma Virus (“HPV”) vaccine and a single case of PV found. “Thus, any evidence attempting to link pemphigus to the vaccine for HBV, or other immunization, is extremely limited.” Resp. Ex. C at 4; Resp. Ex. C Tab 7;⁵¹ Resp. Ex. C Tab 8;⁵² Resp. Ex. C Tab 9;⁵³ Resp. Ex. C Tab 10;⁵⁴ Tr. 153.

Addressing *Berkun et al.*, a single case study of PV following HBV vaccine, Dr. Simpson noted the authors still recommended that PV patients receive non-live vaccines, which would be ill advised if HBV vaccine cross-reactivity was “an established factor in the pathogenesis of pemphigus or flaring of the disease.” Resp. Ex. C at 5; Resp. Ex. C Tab 1.⁵⁵ He also suggested that the *Berkun et al.* authors recognized the limitation of their case study by titling it “Coincidence or Causality?”. Tr. 154; Resp. Ex. C Tab 1.⁵⁶

Dr. Simpson agreed that *Tavakolpour* discussed potential triggers for pemphigus and included vaccines, foods, stress, pesticides, and sun exposure, but “no clear etiology has been established for these diseases.” Resp. Ex. C at 5; Resp. Ex. C Tab 12;⁵⁷ Tr. 116-17. He added that lisinopril was also included in the list of “major reported trigger factors”. *Id.* The author acknowledged a link between vaccines and pemphigus in various case reports, but only *Berkun et al.* reported on an HBV vaccine which was temporally followed by pemphigus. Tr. 116-17, 155-56. The other case reports involved other vaccines and are, therefore, irrelevant in Dr. Simpson’s opinion. Tr. 117, 133. *Tavakolpour* concluded that there was limited evidence that vaccines could trigger PV with a need for greater clarification, which Dr. Simpson interpreted as indicative of a lack of a reliable link between any vaccine and pemphigus has been established. Tr. 117; Resp. Ex. C Tab 12.

At hearing, I pointed out to Dr. Simpson that *Tavkolpour* did not recommend HBV vaccine for PV patients, only influenza, H1N1, tetanus, and pneumococcal. Tr. 118; Resp. Ex. C Tab 12 at

⁵¹ G.J. Bellaney & R.J.G. Rycroft, *Pemphigus Vulgaris Following a Hyperimmune Response to Typhoid Booster*, 21 CLINICAL AND EXPERIMENTAL DERMATOLOGY 434 (1996), filed as “Resp. Ex. C Tab 7”.

⁵² Basak Yalcin & Nuran Alli, *Letter to the Editor: Pemphigus Vulgaris Following Antirabies Vaccination*, 34 J. OF DERMATOLOGY 734 (2007), filed as “Resp. Ex. C Tab 8”.

⁵³ Matthew Muellenhoff, D.O. et al., *Oral Pemphigus Vulgaris After Anthrax Vaccine Administration: Association or Coincidence?*, 50 J. OF THE AM. ACAD. OF DERMATOLOGY 136 (2004), filed as “Resp. Ex. C Tab 9”.

⁵⁴ A. Hviid et al., *Human Papillomavirus Vaccination of Adult Women and Risk of Autoimmune and Neurological Diseases*, 283 J. OF INTERNAL MEDICINE 154 (2018), filed as “Resp. Ex. C Tab 10”.

⁵⁵ Berkun et al., *supra* note 4.

⁵⁶ *Id.*

⁵⁷ Tavakolpour, *supra* note 38.

3.⁵⁸ He agreed that was true in 2018 when the article was published but believed HBV vaccine is now recommended. Tr. 118. He stated that *Laniosz et al.*, an article in the International Journal of Dermatology, recommended all non-live immunization (like HBV vaccine) for patients on immunosuppressive medication for autoimmune bullous dermatoses, a broader category of pemphigus. Tr. 127-28; Resp. Ex. C Tab 11.⁵⁹ The article noted that “HBV vaccination is safe for immunosuppressed individuals” because it is not a live vaccine. Tr. 127-28; Resp. Ex. C Tab 11 at 3. He acknowledged that *Laniosz et al.* stated, “[r]arely, pemphigus and (childhood) pemphigoid have reportedly developed after hepatitis B immunization”, but Dr. Simpson claimed the association was only temporal. Tr. 128; Resp. Ex. C Tab 11 at 4, citing Resp. Ex. C Tab 1.⁶⁰

Dr. Simpson referenced *Kasperkiewicz et al.* as instructive on the etiology of pemphigus, as it did not include any vaccine as causal. Tr. 119; Resp. Ex. C Tab 14.⁶¹ He acknowledged that *Kasperkiewicz et al.* also discussed *De La Fuente* involving bullous pemphigoid, but stated he did not read the article because bullous pemphigoid is a different disease with different pathology and therefore irrelevant to this case. Tr. 114, 128-29.

Dr. Simpson explained that *Kridin et al.*, examined HBV infection not vaccination and is not applicable because “[w]e know for a fact that HBV *vaccination* induces different antibody formation than with HBV *infection*.” Resp. Ex. G at 1 (emphasis in original); Resp. Ex. C at 7; Resp. Ex. C Tab 2;⁶² Tr. 135, 137, 157. HBV virus causes the development of core antibodies while HBV vaccination causes the development of surface antibodies—not core antibodies. Resp. Ex. G at 1. Additionally, *Kridin et al.* is a cross sectional study meaning the data comes from a single snapshot in time, rather than a prospective study involving the passage of time required to calculate incidence rate. *Id.*; Tr. 133-34. A major weakness in the study was a lack of diagnostic specificity, as well as its inability to assess whether patients first had PV or HBV infection, which is important because people may have contracted HBV infection due to being immunosuppressed from PV treatment. Tr. 134-36, 157; Resp. Ex. G at 2; Resp. Ex. C Tab 2.⁶³

Petitioner also relied on *Nikkels et al.*, which summarized skin reactions reported in association with various vaccinations and included PV cases after typhoid booster, flu vaccine, and combination Hep A/B vaccine. It did not provide any additional cases of pemphigus associated with the HBV vaccine. Resp. Ex. C at 7; Resp. Ex. C Tab 16;⁶⁴ Resp. Ex. C Tab 7;⁶⁵ Resp. Ex. C Tab 17;⁶⁶ Resp. Ex. E at 2-3. Dr. Simpson claimed a combination Hep A/B vaccine is a different exposure than the Hep B alone. Tr. 137-39. The article contained a Table, which listed adverse reactions after Hep A and B vaccines, which did not include PV. Tr. 139; Resp. Ex. C Tab 16 at

⁵⁸ *Id.*

⁵⁹ Valerie Laniosz et al., *Literature-Based Immunization Recommendations for Patients Requiring Immunosuppressive Medications for Autoimmune Bullous Dermatoses*, 55 INT’L J. OF DERMATOLOGY 599 (2016), filed as “Resp. Ex. C Tab 11”.

⁶⁰ Berkun et al., *supra* note 4.

⁶¹ Michael Kasperkiewicz et al., *Pemphigus*, 3 NATURE REVIEWS DISEASE PRIMERS 17026 (2017), filed as “Resp. Ex. A Tab 1” and “Resp. Ex. C Tab 14”.

⁶² Kridin et al., *supra* note 5.

⁶³ *Id.*

⁶⁴ Nikkels et al., *supra* note 28.

⁶⁵ Bellanay & Rycroft, *supra* note 51.

⁶⁶ Michele D. Mignogna, M.D., D.D.S. et al., *Pemphigus Induction by Influenza Vaccination*, 39 INT’L J. OF DERMATOLOGY 795 (2000), filed as “Resp. Ex. C Tab 17”.

7, Table V. He also discussed a different Table that did include PV, but it was after influenza vaccine, a different exposure as discussed in *Mignogna et al.* Tr. 139-40; Resp. Ex. C Tab 16 at 7, Table VI; Resp. Ex. C Tab 17.

I pointed out to Dr. Simpson that the first paragraph in *Nikkels et al.* states, “[v]accines are given to induce or boost a specific immune response in order to prevent or to treat specific diseases. Although vaccination against viral and bacterial agents is conducted on a large scale worldwide, the occurrence of cutaneous adverse effects is quite rare compared with the prevalence of drug reactions.” Resp. Ex. C Tab 16 at 1.⁶⁷ Dr. Simpson conceded that pemphigus is a rare disease, and thus, “it is not surprising that there are rare reports of any known or suspected trigger.” Tr. 141. He added that vaccines are “specifically designed to induce an immune response”. Tr. 141. He further agreed that “[a]ny intervention that we do to a patient can have an adverse outcome, whether that’s an injection, a procedure, a vaccine, a medication”, but he would not tell a patient there was a risk of pemphigus from an HBV vaccine because there is no reliable evidence to support that. Tr. 141-42.

Further, while *Davidson & Diamond* reviewed autoimmunity and proposed mechanisms of pathogenesis of various diseases, their discussion involved a hypothesis of an autoimmune trigger for an endemic form of pemphigus common in Brazil. The study was on pemphigus foliaceus—not vulgaris—and not related to any vaccination. Dr. Simpson conceded that the authors discussed drugs as a potential inducer of autoimmunity by the formation of a complex called hapten with a self-protein, leading to self-reactive antibody generation. Resp. Ex. E at 2; Pet. Ex. 21 at 4.⁶⁸

Dr. Simpson contended that despite case reports of PV following vaccination and “while a link has been theorized, it remains an untested hypothesis” and not an established trigger to experts in the field. Resp. Ex. C at 5. He added that HBV vaccine is widely administered in the U.S. and recommended by the CDC for healthcare workers, so the possibility exists to assess the vaccine’s association with pemphigus in a more robust fashion; but at this time, no statistically testable, population-scale, unbiased data analysis is available. *Id.* at 5.

Therefore, Dr. Simpson concluded that there is a lack of large-scale, unbiased clinical data assessing whether a statistically significant relationship exists between the HBV vaccine and PV. As such, Dr. Simpson stated that one cannot state it is more likely than not that the HBV vaccine caused petitioner’s PV here. Tr. 112, 131, 132, 143-44, 154, 158; Resp. Ex. C at 7-8; Resp. Ex. C Tab 14;⁶⁹ Resp. Ex. E at 3; Resp. Ex. G at 2.

Unlike the HBV vaccine, medications like ACE inhibitors are mentioned in textbooks and the literature as potential triggers for PV. Tr. 161-63. He cited in-vitro studies of ACE inhibitors that have shown a direct effect on the ability of keratinocytes to stick to one another to support his conclusion that medication was a more likely cause of petitioner’s PV than was the vaccine. Tr. 144-45.

⁶⁷ Nikkels et al., *supra* note 28.

⁶⁸ Davidson & Diamond, *supra* note 23.

⁶⁹ Kasperkiewicz et al., *supra* note 61.

He agreed that challenge-rechallenge can be used as evidence to make a clinical diagnosis. Tr. 163. Dr. Simpson largely deferred to the immunologists on the immunology, but he stated that “[j]ust because you get some response with a vaccine and a similar response with the infection, it does not mean that they are equivalent exposures.” Tr. 163-66.

b. Prong II

Dr. Simpson summarized petitioner’s history to include an HBV vaccine on December 6, 2012, with negative protective antibodies on September 4, 2014, requiring two additional HBV vaccines on October 28, 2014 and April 3, 2015. Serology testing on May 15, 2015 showed protective antibodies. Resp. Ex. C at 2; *see* Pet. Ex. 1 at 1, 9; Pet. Ex. 5. Petitioner’s diagnosis of PV was confirmed by skin biopsies and positive DSG autoantibodies following the third HBV vaccine. Resp. Ex. C at 2, 4; Pet. Ex. 3 at 3; Pet. Ex. 7 at 1; Pet. Ex. 1 at 13.

Dr. Simpson acknowledged that it was Dr. Norris’ opinion that the rash and shoulder lesion petitioner described after the first and second HBV vaccines could have been early PV. However, Dr. Simpson noted that no evaluation or skin biopsy was performed, so the etiology is unknown. Resp. Ex. C at 6; Resp. Ex. E at 2. He also claimed that Dr. Byers admitted that petitioner had no anti-hepatitis B antibodies when he developed the rash lesion, causing a critical discrepancy. If the gum bleeding in 2013 and later rashes were caused by the vaccines, then the vaccine worked “well enough to produce off-target anti-[DSG] antibodies to cause clinical lesions of PV,” but not well enough to produce HBV surface antibodies which it was specifically engineered to do. This is “*highly unlikely*”.⁷⁰ Resp. Ex. G at 2 (emphasis in original).

He submitted that, alternatively, the lesion could have been a mild episode of herpes zoster (shingles), which was recurrent. Tr. 123; Resp. Ex. C at 6; Pet. Ex. 14 at 11 (documenting petitioner’s herpes zoster). Dr. Simpson explained that shingles is a commonly known trigger of skin disease. Tr. 123-24; Resp. Ex. C Tab 12 at 3.⁷¹ I pointed out to Dr. Simpson, and he then agreed, that the reference to shingles in the medical records was to Dr. Norris in 2017 after petitioner had been diagnosed with PV when he suspected he had shingles and was experiencing a pemphigus exacerbation. Tr. 125.

Dr. Simpson stated that petitioner’s medical records document that he suffered from various oral health issues common in pemphigus patients. Many patients report significant gum disease, oral surgeries, or other dental procedures prior to being diagnosed with pemphigus, and oral findings are typically the initial presentation of PV. Tr. 120; Resp. Ex. C at 3. Damage to mucous membranes could lead to antigen exposure of DSG and subsequent autoantibody development. Resp. Ex. C at 6. He referenced *Daneshpazhooh et al.* in which the authors discussed tissue trauma, including dental procedures, as a trigger for pemphigus. The authors identified thirty-six patients with PV who had a history of some sort of tissue trauma. Tr. 120-21; Resp. Ex.

⁷⁰ The evidence shows that petitioner developed a rash on his chest after the first HBV and a shoulder lesion after the second HBV. FH Tr. 6-7, 47. However, hepatitis antibody tests were performed after the first and third HBV vaccine. Pet. Ex. 1 at 1, 9. The test after the first vaccine did not show antibodies, but the test after the third vaccine did. Therefore, whether petitioner had antibodies to Hepatitis B after the second HBV vaccination is unknown.

⁷¹ Tavakolpour, *supra* note 38.

E at 1-2; Resp. Ex. E Tab 2 at 4, Table 1;⁷² Resp. Ex. G at 2.

Dr. Simpson contended that it is more likely that tissue trauma led to exposure of neo-antigens in the gum tissue, resulting in the formation of pemphigus autoantibodies. Resp. Ex. E at 1; Resp. Ex. G at 2. He submitted that petitioner's dental issues of heavy plaque and bleeding gums on February 19, 2013 could have been early signs of PV or an episode of tissue trauma due to a difficult cleaning that triggered his PV. Resp. Ex. C at 2; Pet. Ex. 9 at 1.

Dr. Simpson added that medications are believed to induce PV. Resp. Ex. C at 5-6. He believed that petitioner suffered some kind of rash after he started lisinopril, which was discontinued at some point. As it was the only medication listed in the record, Dr. Simpson looked further into it as a trigger of pemphigus. Tr. 122. Dr. Simpson stated that there is as much evidence supporting a link between PV and lisinopril as exists supporting a link between PV and HBV vaccine, as both are supported by only one case report. Resp. Ex. C at 5-6. In a subsequent report, Dr. Simpson added that lisinopril has been linked to pemphigus foliaceus with specific autoantibodies found in the skin. Resp. Ex. G at 2; Resp. Ex. C Tab 15;⁷³ Tr. 122. He also cited to *Pietkiewicz et al.*, which concluded that drugs as a trigger should be considered in every case of newly diagnosed or exacerbated pemphigus. Resp. Ex. G at 2; Resp. Ex. C Tab 13.⁷⁴

Dr. Simpson disagreed that petitioner's medical history showed a clear challenge-rechallenge, stating that the records show a "less severe phenotypic outcome" after the second vaccine than the first, so it was not a step wise progression in severity. Tr. 145-46. He submitted that the skin lesions after the first and second HBV vaccines were never examined or biopsied by a dermatologist and resolved quickly, which does not occur with PV lesions in his experience. Tr. 146; Resp. Ex. E at 2. Dr. Simpson stated that petitioner's experts accept that the symptoms petitioner described after each vaccine were signs of PV, but "we don't know that it was pemphigus". Tr. 146-47. Noting again that testing showed petitioner did not have hepatitis B antibodies, Dr. Simpson stated that it is unlikely that a vaccine designed to induce antibodies would not do so to an effective degree to confer immunity but would induce enough DSG antibodies to cause quite a severe reaction in the gums and the skin. Tr. 146-47. Therefore, Dr. Simpson was not convinced based on the sequence of events and negative antibody testing for HBV that there was challenge-rechallenge. Tr. 147.

I pointed out to Dr. Simpson that the antibody level following the first two HBV vaccines is unknown because there was no reference range provided on the testing. Tr. 147-48; Pet. Ex. 1 at 1. Further, the article he filed on anthrax showed a patient who developed PV after the first shot, had a less severe reaction after the second with no lesions, and then a more severe reaction after the third shot, suggesting that the reaction need not be progressively worse each time. Tr. 148. Dr. Simpson deferred to the immunologists but stated, as a dermatologist, it did not sound like each

⁷² Maryam Daneshpazhooh et al., *Trauma-Induced Pemphigus: A Case Series of 36 Patients*, 14 J. OF THE GERMAN SOC'Y OF DERMATOLOGY 166 (2016), filed as "Resp. Ex. E Tab 2".

⁷³ CRS Patterson & MG Davies, *Pemphigus Foliaceus: An Adverse Reaction to Lisinopril*, 15 J. OF DERMATOLOGICAL TREATMENT 60 (2004), filed as "Resp. Ex. C Tab 15".

⁷⁴ Pawel Pietkiewicz et al., *A Retrospective Study of Antihypertensives in Pemphigus: A Still Uncharted Odyssey Particularly Between Thiols, Amides and Phenols*, 11 ARCHIVES OF MED. SCI. 1021 (2015), filed as "Resp. Ex. C Tab 13".

successive vaccine petitioner received led to a more severe reaction, which was what petitioner's experts stated, and he believed that "clarification is important." Tr. 148-49.

Dr. Simpson also took issue with petitioner's HBV vaccinations being given on December 6, 2012, October 28, 2014 and April 3, 2015, claiming they were not given on the recommended schedule for adults with such a long interval between the first and second vaccine. Resp. Ex. C. at 6. The relevance of this was not articulated.

Dr. Simpson also gave little credence to petitioner's treating physicians' (one being Dr. Norris) conclusions that the HBV vaccine caused petitioner's PV because no scientific evidence was cited in support of their assertions, and "even physicians are subject to the temptation to attribute causation to a correlation." Resp. Ex. E at 2.

I asked Dr. Simpson if one of his patients reported a rash on his chest following his first HBV vaccine that went away, then developed a blister on his shoulder after the second vaccine, would he suggest a third vaccine? Tr. 149. Dr. Simpson stated such a hypothetical is hard to answer because the patient's history was unknown. Tr. 149. Further, he would have to consider recall bias where a patient places undue recollection on certain things upon subsequent knowledge. Tr. 150. The vaccine may stand out in their mind rather than the ibuprofen they took, the food they ate, or the minor cold they had. Tr. 150, 151. Thus, it is difficult to rule all other possible exposures that may have been related to the rashes or lesions. Tr. 151.

The question was revisited on cross examination when he was asked whether he would recommend a fourth vaccine to that patient. He refused to answer stating "It would be inappropriate as a physician to speculate on that type of a hypothetical scenario. I just simply can't do it." Tr. 163-64. He added that he recommends all vaccines his patients are eligible for and that are not contraindicated for them. Tr. 165.

In sum, Dr. Simpson pointed to various alternative exposures that preceded petitioner's PV as the more likely cause of his PV. Resp. Ex. E at 3. Further, the cross-sectional study referenced was irrelevant because petitioner did not have a history of HBV infection.⁷⁵ Resp. Ex. C at 7; Resp. Ex. A Tab 4.⁷⁶ Other exposures such as infection with shingles, medication such as lisinopril, and/or tissue trauma from gingival disease or the trauma from dental manipulation are just as likely triggers for petitioner's PV. Resp. Ex. C at 7.

c. Prong III

Dr. Simpson did not discuss *Althen* Prong III.

III. Discussion

A. Standard for Adjudication

⁷⁵ Petitioner had hepatitis as a child. FH Tr. 42-43.

⁷⁶ Kridin et al., *supra* note 5.

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a “Table” injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). “In such a case, causation is presumed.” *Capizzano v. Sec’y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); see § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an “off-Table” injury, which requires that the petitioner “prove by a preponderance of the evidence that the vaccine at issue caused the injury.” *Capizzano*, 440 F.3d at 1320; see § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec’y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a “substantial factor” and a “but for” cause of the injury is sufficient for recovery. See *Pafford v. Sec’y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec’y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).⁷⁷

To prove causation for an “off-Table” injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec’y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury “by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” *Id.* at 1278. Together, these prongs must show “that the vaccine was ‘not only a but-for cause of the injury but also a substantial factor in bringing about the injury.’” *Stone v. Sec’y of Health & Human Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with “no hard and fast per se scientific or medical rules.” *Knudsen v. Sec’y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify “specific biological mechanisms” to establish causation, nor are they required to present “epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities.” *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). “[C]lose calls regarding causation are resolved in favor of injured claimants.” *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioner to provide a “reputable medical theory” demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner’s “theory of causation must be supported by a ‘reputable medical or scientific explanation.’” *Andreu ex rel. Andreu v. Sec’y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be “legally probable, not medically or scientifically certain.” *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548). Nevertheless, “petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature.” *LaLonde v. Sec’y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

⁷⁷ The Vaccine Act also requires petitioners to show by preponderant evidence the vaccinee suffered from the “residual effects or complications” of the alleged vaccine-related injury for more than six months, died from the alleged vaccine-related injury, or required inpatient hospitalization and surgical intervention as a result of the alleged vaccine-related injury. § 11(c)(1)(D). It is undisputed that this requirement is satisfied in this case.

The second *Althen* prong requires proof of a “logical sequence of cause and effect.” *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioner must show “that it did so in [this] particular case.” *Hodges v. Sec’y of Health & Human Servs.*, 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). “A reputable medical or scientific explanation must support this logical sequence of cause and effect,” *id.* at 961 (citation omitted), and “treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury,” *Paluck v. Sec’y of Health & Human Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375). Petitioner is not, however, required “to eliminate alternative causes as part of establishing [their] *prima facie* case.” *Doe v. Sec’y of Health & Human Servs.*, 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec’y of Health & Human Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a “petitioner does not bear the burden of eliminating alternative independent potential causes”).

To satisfy the third *Althen* prong, petitioner must establish a “proximate temporal relationship” between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This “requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder’s etiology, it is medically acceptable to infer causation-in-fact.” *De Bazan v. Sec’y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, “a petitioner’s failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause.” *Id.* However, “cases in which onset is too soon” also fail this prong; “in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked.” *Id.*; *see also Locane v. Sec’y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) (“[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.”).

B. Legal Standard Regarding Fact Finding

The process for making determinations in Vaccine Program cases regarding factual issues begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are generally considered to be more trustworthy. *Cucuras v. Sec’y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993); *but see Kirby v. Sec’y of Health & Human Servs.*, 993 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying that *Cucuras* does not stand for proposition that medical records are presumptively accurate and complete). While not presumed to be complete and accurate, medical records made while seeking treatment are generally afforded more weight than statements made by petitioner after-the-fact. *See Gerami v. Sec’y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013) (finding that contemporaneously documented medical evidence was more persuasive than the letter prepared for litigation purposes), *mot. for rev. denied*, 127 Fed. Cl. 299 (2014). Indeed, “where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight.” *Campbell ex rel. Campbell v. Sec’y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948).

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining facts such as the onset of a petitioner's symptoms. *Vallenzi v. Sec'y of Health & Human Servs.*, No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); *see also Eng v. Sec'y of Health & Human Servs.*, No. 90-175V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) (explaining that § 13(b)(2) "must be construed so as to give effect to § 13(b)(1) which directs the special master or court to consider the medical record...but does not require the special master or court to be bound by them"); *see also Burns v. Sec'y of Health & Human Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993) (holding that it is within the special master's discretion to determine whether to afford greater weight to medical records or to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is rational).

There are situations in which compelling oral testimony may be more persuasive than written records. *See Campbell*, 69 Fed. Cl. at 779. When witness testimony contradicts medical records, such testimony must be consistent, clear, cogent, and compelling to be persuasive. *See Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (vacated on other grounds, *Sanchez by & through Sanchez v. Sec'y of Health & Human Servs.*, No. 2019-1753, 2020 WL 1685554 (Fed. Cir. Apr. 7, 2020), *review denied*, *Sanchez by & through Sanchez v. Sec'y of Health & Hum. Servs.*, 152 Fed. Cl. 782 (2021)) (quoting *Blutstein v. Sec'y of Health & Human Servs.*, No. 90-2808V, 1998 WL 408611, at *85 (Fed. Cl. Spec. Mstr. June 30, 1998)); *see, e.g., Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose "memory was sound" and "recollections were consistent with the other factual evidence"). Special masters may also consider other types of evidence, such as unsworn statements, on the grounds that the Vaccine Program was designed to have "flexible and informal standards of admissibility of evidence." 42 U.S.C. § 300aa-12(d)(2)(B); *see also Munn v. Sec'y of Health & Human Servs.*, 970 F.2d 863, 873 (Fed. Cir. 1992).

In short, "the record as a whole" must be considered. § 13(a).

C. Evaluating Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Id.* at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and

the relative persuasiveness of their competing theories.” *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert’s conclusion “connected to existing data only by the *ipse dixit* of the expert,” especially if “there is simply too great an analytical gap between the data and the opinion proffered.” *Snyder ex rel. Snyder v. Sec’y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec’y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) (“We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision.”); *Simanski v. Sec’y of Health & Human Servs.*, 115 Fed. Cl. 407, 436 (2014) (“[A] Special Master is ‘not required to discuss every piece of evidence or testimony in her decision.’” (citation omitted)), *aff’d*, 601 F. App’x 982 (Fed. Cir. 2015).

IV. Causation Analysis

Because petitioner does not allege an injury listed on the Vaccine Injury Table, his claim is classified as “off-Table.” As noted above, for petitioner to prevail on an “off-Table” claim, he must show by preponderant evidence that his pemphigus vulgaris resulted from the vaccination at issue. *Capizzano*, 440 F.3d at 1320. Doing so shifts the burden to respondent to show that the injury was caused by factors unrelated to the vaccinations. *Deribeaux ex rel. Deribeaux v. Sec’y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013).

A. Symptoms Following Each of Petitioner’s Three HBV Vaccinations

There is no dispute that petitioner has PV. Despite petitioner’s petition and pre-hearing submission alleging only the April 3, 2015 HBV vaccine as causal to petitioner’s PV, both of petitioner’s experts argued at hearing and in their reports that all three HBV vaccines contributed to petitioner’s PV via a challenge-rechallenge theory. *See* Petition; Pet. Br. at 1-2; Pet. Ex. 20 at 3; Pet. Ex. 23 at 5; Tr. 21, 30-31, 69, 78. Therefore, an analysis of the available evidence associated with all three HBV vaccines must be undertaken.

Petitioner received the first HBV vaccine on December 6, 2012. Pet. Ex. 5 at 1. At the Fact Hearing, petitioner testified to a nonspecific rash on his chest after the first HBV vaccine in 2012 that went away on its own. FH Tr. 6, 47. However, petitioner initially affirmed that he developed a rash and lesion on his shoulder following the *second* HBV vaccination. Pet. Ex. 6 at 1. He noted in his affidavit that he did not notice any symptoms following the first HBV vaccine. *Id.*

Roughly two months after the first HBV vaccine, petitioner presented to the dentist with heavy gingival bleeding. Pet. Ex. 9 at 1. The record specifically documents that a cleaning was completed with a hand instrument. *Id.* There were no dental visits for the next seventeen months,

at which time petitioner presented for crowns, and gum inflammation was noted. *Id.* The record did not document gingival bleeding at this visit.

Blood work on September 4, 2014 failed to show hepatitis B antibodies following the first HBV vaccination. Pet. Ex. 1 at 1. Thus, petitioner required further HBV vaccination, and he received his second vaccine on October 28, 2014. Pet. Ex. 5 at 1.

Following the second vaccination, petitioner testified that a lesion developed on his shoulder. He asked his colleague Dr. Massey to do a biopsy of the lesion. However, the lesion resolved on its own, so the biopsy was not done. FH Tr. 6-7. Dr. Massey's affidavit supports this contention. In his affidavit, Dr. Massey affirmed that petitioner approached him to look at his shoulder; they planned on doing a biopsy, but that was never performed. Pet. Ex. 12.

The records filed do not show any testing for Hep B antibodies after the second HBV vaccination. Petitioner received the third HBV vaccine on April 3, 2015. Pet. Ex. 5 at 1.

After the third HBV vaccine, petitioner developed a host of symptoms consistent with PV. FH Tr. 24, 56-57, 65. He had tenderness with bleeding gums on the right side of his mouth. When the gum issues failed to resolve, he made a dentist appointment. FH Tr. 8-10, 22, 24, 55-56, 62-63. On June 23, 2015, he presented to the dentist, who noted that his "gums [were] tender and bleeding on the [right] side top and bottom." Pet. Ex. 9 at 2; FH Tr. 21. Five days later, an abscess developed that required an emergency root canal. FH Tr. 21, 44-45, 64-65; Pet. Ex. 9 at 2. Once the abscess resolved, petitioner was able to clearly see a lesion on his gums with a flashlight. FH Tr. 75-76.

Also, after the third HBV vaccine, around May 2015, petitioner began having nosebleeds, developed an eye lesion that looked like a sty and a sore on his nose that looked like a pimple, and noticed a rash on the top of his head. At the time, he thought the rash was due to his surgical headlamp. FH Tr. 8-9, 11, 18-19, 71-72, 74. Petitioner spoke with his colleague Dr. Blomstedt about the rash, and Dr. Blomstedt gave petitioner samples of steroid and antibiotic creams to try, which petitioner used for roughly one month. FH Tr. 11-12, 16, 77; Pet. Ex. 11. Petitioner ultimately told Dr. Blomstedt that he needed biopsies when the rash did not resolve, which were performed on August 24, 2015. Tr. 17, 19-21, 65; Pet. Ex. 3 at 1. Dr. Blomstedt's notes on August 24, 2015 documented lesions on the right lower eyelid and the right side of petitioner's nose. FH Tr. 17, 53-54; Pet. Ex. 3 at 1. Biopsies taken from the nose and scalp resulted in a differential diagnosis including pemphigus vulgaris. Pet. Ex. 3 at 3; FH Tr. 19-21. Three days later, petitioner had a biopsy of the lesion on his lower eyelid, which also raised concern for pemphigus. Pet. Ex. 7 at 1, 17.

Petitioner presented to Drs. Norris and Caldwell at the University of Colorado on September 24, 2015 "for evaluation of pruritic and painful rash of 2 months duration involving the scalp, face and chest. Lesions are crusted over. Rash is *worsening over time*." Pet. Ex. 4 at 3 (emphasis added). It was noted that petitioner reported receiving the Hep B vaccination series at the time he developed the rash on his scalp, face, and chest. Pet. Ex. 4 at 3; FH Tr. 33-35. Petitioner underwent a shave biopsy on his left shoulder, which was consistent with pemphigus but did not clearly distinguish pemphigus vulgaris from pemphigus foliaceus. Pet. Ex. 4 at 4, 16.

By October 22, 2015, the diagnosis was pemphigus vulgaris due to oral involvement and DSG 3 positivity. The record noted that “[S]ymptoms started with erythema around a seborrheic keratosis on his upper chest following the second round of HBV series, but resolved within a few weeks. After receiving the third round in 7/2015, he noted diffuse onset of erosions on the scalp, face, and chest...”.⁷⁸ *Id.* Dr. Norris opined that the pemphigus was triggered by the HBV vaccination series, given the time of onset. Pet. Ex. 4 at 22, 35. Dr. Norris wrote a letter on the same date, stating that petitioner’s PV was “suspected to be precipitated from hepatitis B vaccination.” *Id.* at 30.

Details of when symptoms appeared are inconsistent at times. *See* Pet. Ex. 6 at 1; FH Tr. 47. Because petitioner is a doctor, he was able to self-treat and consult informally with various colleagues. Therefore, he did not always seek formal medical treatment, explaining why medical records do not exist. Nevertheless, the medical records from later visits and corroborating affidavits are telling, with the evidence as a whole demonstrating that petitioner had symptoms suggestive of PV within roughly one month following the second HBV vaccine. Pet. Ex. 12 (Dr. Massey affirming that petitioner approached him about his shoulder lesion around December 2014—roughly one month after the second HBV vaccine); Pet. Ex. 4 at 23 (petitioner reporting to Dermatology on October 22, 2015 that his “[s]ymptoms started with erythema around a seborrheic keratosis on his upper chest following the second round of HBV series, but resolved within a few weeks); Pet. Ex. 3 at 1 (Dr. Blomstedt noting on August 24, 2015 that petitioner had a “chronic” rash on his scalp); Pet. Ex. 6 at 1 (petitioner stating in his affidavit that he developed a rash and lesion on his shoulder following the second HBV vaccination). Petitioner’s symptoms resolved until approximately one month after the third HBV vaccine, at which time he developed a host of PV symptoms, including bleeding gums and lesions on his scalp, eyelid, nose, and gums. FH Tr. 8-11, 17-22, 24, 33-35, 44-45, 55-56, 62-65, 71-72, 74, 75-76; Pet. Ex. 3 at 1, 3; Pet. Ex. 4 at 3-4, 16, 22, 30, 35; Pet. Ex. 7 at 1, 17; Pet. Ex. 9 at 2; Pet. Ex. 11.

However, the evidence is insufficient to show that petitioner developed PV symptoms after the first HBV vaccine. *See* Pet. Ex. 6 at 1 (petitioner affirmed that he did not notice symptoms following his first HBV vaccine); Pet. Ex. 1 at 1 (testing showed that petitioner failed to show hepatitis B antibodies following the first HBV vaccination). Dr. Levinson and Dr. Simpson aptly pointed out that it is highly unlikely that petitioner would test negative for Hep B antibodies while having an adverse immune response to the first HBV vaccine. Resp. Ex. A at 6; Resp. Ex. G at 2; Resp. Ex. H at 3; Tr. 146-47, 182.

Accordingly, I find that the evidence as a whole supports that petitioner experienced a reaction after the second HBV vaccine including a rash and lesion suggestive of PV that resolved, with the third HBV vaccine triggering full activation and leading to a diagnosis of PV.

B. *Althen* Analysis

a. Prong I: Petitioner Has Proffered a Reputable Medical Theory

⁷⁸ *See supra* note 19.

Under *Althen* prong one, petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. *Andreu*, 569 F.3d at 1375; *Pafford*, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. *Boatmon*, 941 F.3d at 1359; *see also Knudsen*, 35 F.3d at 548; *Veryzer v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioner relies upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. *See Broekelschen*, 618 F.3d at 1347 ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); *Perreira v. Sec'y of Health & Human Servs.*, 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing *Fehrs v. United States*, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds that petitioner has proven by preponderant evidence that the HBV vaccination can trigger PV in a genetically susceptible individual through the immune-mediated processes of epitope spreading and bystander activation, as described by Drs. Byers and Norris.

The experts agreed that pemphigus is a rare autoimmune blistering disease caused by autoantibodies against proteins DSG 1 and 3. Pet. Ex. 15 at 1; Pet. Ex. 17 at 1;⁷⁹ Pet. Ex. 18 at 1;⁸⁰ Pet. Ex. 19 at 1;⁸¹ Pet. Ex. 23 at 3; Pet. Ex. 45 at 1;⁸² Resp. Ex. A at 3-4; Resp. Ex. C at 3-4. In PV, circulating antibodies attack the skin and mucous membranes, resulting in the loss of cohesion between keratinocytes in the skin and creating open sores that multiply across the body and oral cavity. Pet. Ex. 15 at 1; Pet. Ex. 23 at 3; Resp. Ex. A at 3-4; Resp. Ex. C at 3-4. Dr. Norris explained that the disease is 70-95% fatal if not treated due to infections from the skin's failure to protect. Pet. Ex. 15 at 1. They agreed that the production of autoreactive antibodies to DSG 1 and 3 is genetically determined, and the onset may have a variety of triggers including stress, bacterial or viral infections, ultraviolet radiation, tissue trauma, certain medications, and chemicals. Pet. Ex. 15 at 2; Pet. Ex. 21;⁸³ Pet. Ex. 20 at 3; Resp. Ex. C at 5; Resp. Ex. E at 1.

The experts generally agreed that the literature shows that the etiology of PV is unknown but has occasionally been associated with antecedent factors, such as medications, infections, or neoplasms and that case studies have reported PV following viral and bacterial vaccinations. Pet. Ex. 19 at 1-2.⁸⁴ *Kridin et al.* explained that "...pemphigus develops due to interaction between predisposing genetic and environmental factors." Pet. Ex. 18 at 1;⁸⁵ *see also* Pet. Ex. 45 at 1.⁸⁶

The experts further agreed that vaccinations are designed to activate the innate immune system, which responds by producing pro-inflammatory cytokines that attract T cells that travel to

⁷⁹ Berkun et al., *supra* note 4.

⁸⁰ Kridin et al., *supra* note 5.

⁸¹ De Simone et al., *supra* note 6.

⁸² Masjedi et al., *supra* note 7.

⁸³ Davidson & Diamond, *supra* note 23.

⁸⁴ De Simone et al., *supra* note 6.

⁸⁵ Kridin et al., *supra* note 5.

⁸⁶ Masjedi et al., *supra* note 7.

local and regional lymph nodes, ultimately inducing antigen-specific adaptive immunity. Pet. Ex. 20 at 2; Pet. Ex. 23 at 5; Resp. Ex. H at 3; Tr. 11-12, 17-19, 141.

Dr. Norris and Byers opined that the mechanisms by which an autoimmune disease can be triggered include epitope spreading and bystander activation. Epitope spreading is where damaged tissue produces cryptotopes that are antigenic and activate B and T cells, producing inflammation and further tissue damage, which then activates self-reactive antigens causing an immune reaction. Pet. Ex. 20 at 2; Pet. Ex. 23 at 3-4. Bystander activation is an exaggerated immune response to a foreign antigen that induces local tissue inflammation and stimulation of otherwise normal cells, which can result in the release of normally sequestered self-antigens. Pet. Ex. 20 at 3; Pet. Ex. 23 at 6; Tr. 18, 61, 68-69, 95. The inflammation may activate previously dormant auto-reactive Th-1 cells that then react against the newly released self-antigens. Factors that may trigger bystander activation and cause PV include friction, local bacterial infection, or ultraviolet radiation. Pet. Ex. 20 at 3.

Dr. Byers added that, normally, invoking existing memory B cells that react with autologous antigens controlled by regulatory T cells occurs without event. However, memory B cells are very sensitive to proinflammatory cytokines produced by vaccines and are critical to their effectiveness. Pet. Ex. 23 at 5. Here, the HBV vaccine produced inflammatory cytokines which activated the autoreactive B cells directed against both DSG 1 and 3. *Id.* The most probable series of events is consistent with bystander activation initiated by the first HBV vaccine, then a rechallenge and epitope spreading after the second HBV vaccine. After the third HBV vaccination, the mature autoreactive B cells produced antibodies that continued to accumulate until no longer controlled. *Id.* at 6.

Petitioner's experts cited several articles in support of their proffered theory, including *Berkun et al.*, which stated that "[t]he associated vaccine most often involved with autoimmunity is the HBV vaccine". Pet. Ex. 20 at 3; Pet. Ex. 15 at 2; Pet. Ex. 17 at 2.⁸⁷ *Berkun et al.* was a case report involving the onset of PV following hepatitis B vaccine, suggesting that "in some cases vaccination may be the triggering factor for pemphigus in genetically predisposed individuals". Pet. Ex. 17.⁸⁸ Dr. Byers pointed to Table I in *Berkun et al.*, which contained a list of autoimmune diseases associated with HBV vaccine and included bullous pemphigoid, which she stated refers to PV. Tr. 14-15, 50-51; Pet. Ex. 17 at 2. Dr. Norris further stated that, theoretically, any vaccine can induce PV or any autoimmune disease, although some vaccines are more likely to do so than others. Tr. 91-92; Pet. Ex. 22 at 7, Table V.⁸⁹

Dr. Norris and Dr. Byers also discussed *Kridin et al.*, which admittedly involved hepatitis B infection, not vaccination, but was a large-scale epidemiological study that found those with pemphigus have a statistically higher prevalence of HBV infection when compared to controls. Tr. 12-13, 89; Pet. Ex. 18;⁹⁰ Pet. Ex. 23 at 3, 4. Dr. Byers explained that "when a vaccine is considered a suspect in an *autoimmune* disease, it is usually agreed that information of autoimmune diseases which occur with the active disease can be used to support an association, because the important

⁸⁷ Berkun et al., *supra* note 4.

⁸⁸ *Id.*

⁸⁹ Nikkels et al., *supra* note 28.

⁹⁰ Kridin et al., *supra* note 5.

epitopes on the vaccine are the same as those on the infective disease.” Pet. Ex. 23 at 4 (emphasis in original); Tr. 57, 62-63. The study included nearly 2,000 patients with PV and nearly 10,000 controls, and the results were statistically significant. Pet. Ex. 23 at 3, 4; Tr. 21-22, 49, 57.

Dr. Norris also referenced *De Simone et al.*, which showed that multiple environmental factors, such as ultraviolet radiation, trauma, drugs, and infections, can trigger autoimmune disease. Tr. 90; Pet. Ex. 19.⁹¹ In *De Simone et al.*, the flu vaccine exacerbated the patient’s PV, providing evidence that a vaccination for a virus can trigger PV symptoms. Tr. 90-91.

Dr. Byers cited *Tavakolpour* to show that various vaccines, including HBV, have been linked to the development of PV. Tr. 22; 25-26; Resp. Ex. C Tab 12 at 7, Figure 1.⁹² She noted *Tavakolpour* concluded that, “Infections stimulate various immune responses (usually Th1 and Th17 associated responses) . . . autoinflammatory diseases induce vigorous immune responses as well as dysfunction of regulatory responses. The promotions of humoral (antibodies) and cellular immune responses are undeniable outcomes of any vaccines, which contribute to the progression of pemphigus.” Tr. 26-28; Resp. Ex. C Tab 12 at 7-8.

Dr. Levinson agreed that Dr. Norris accurately described the role of anti-desmoglein antibodies in the pathogenesis of PV. However, both Drs. Levinson and Simpson argued that Dr. Norris failed to link this mechanism to the HBV vaccine. Resp. Ex. A at 5; Resp. Ex. E at 1; Resp. Ex. F at 1. Dr. Levinson explained that bystander activation has been demonstrated following infection but not after vaccination in otherwise healthy hosts. Resp. Ex. H at 2-3; Tr. 189-93, 201, 203. He did not know if vaccines can cause epitope spreading that leads to the development of autoimmune disease because that has not been investigated. Tr. 202. Likewise, Dr. Simpson stated that Dr. Byers’ discussion of how HBV vaccine could lead to bystander activation and cause PV was not supported by peer-reviewed literature. Resp. Ex. G at 1.

Dr. Levinson relied on *Pacheco et al.* and *Westra et al.* to support his position that vaccines do not cause bystander activation that leads to autoimmunity. Resp. Ex. H Tab 1;⁹³ Resp. Ex. H Tab 2.⁹⁴ *Pacheco et al.* discussed stimulation of the innate immune system by non-specific proinflammatory antigens following vaccination, acknowledging that T cells can non-specifically activate independently due to an adjuvant in the vaccine. Resp. Ex. H Tab 1 at 5. The authors concluded that more studies are needed to understand the role of vaccine-mediated bystander activation in the development of autoimmune disease. *Id.* *Westra et al.* discussed vaccination in patients with autoimmune inflammatory rheumatic diseases (“AIRD”) (such as rheumatoid arthritis, lupus, and Behcet’s syndrome—not bullous skin diseases) but was focused more on the efficacy and safety of vaccinations in these patients who have compromised immune systems due in part to their medications. The authors concluded that vaccination is extremely important in patients with AIRD because they are at a higher risk of infection; at the same time, they noted that vaccination “is complicated by possible decreased efficacy of the vaccine and the risk of exacerbating underlying disease”. *Id.* at 2. Ultimately, *Westra et al.* stated that studies tended to show that vaccinations do not exacerbate underlying AIRDs, but “serious vaccine-attributable

⁹¹ *De Simone et al.*, *supra* note 6.

⁹² *Tavakolpour*, *supra* note 38.

⁹³ *Westra et al.*, *supra* note 44.

⁹⁴ *Pacheco et al.*, *supra* note 43.

conditions are rare” so there is insufficient data to conclude that “vaccination during active disease is safe and efficacious.” *Id.* at 8.

Respondent’s experts argued the literature relied on by petitioner’s experts was insufficient to support a causal link between HBV vaccine and PV. Resp. Ex. A at 5; Resp. Ex. C at 4; Resp. Ex. F at 2. *Berkun et al.* is a case report with a lapse of three months between vaccination and the onset of PV symptoms. Resp. Ex. A at 5; Resp. Ex. C Tab 1 at 2.⁹⁵ Dr. Simpson noted the authors still recommended that PV patients receive non-live vaccines like HBV, which would be ill advised if HBV vaccine cross-reactivity was “an established factor in the pathogenesis of pemphigus or flaring of the disease.” Resp. Ex. C at 5; Resp. Ex. C Tab 1.⁹⁶ *Kridin et al.* discussed PV in persons with chronic HBV infection not HBV vaccination. Resp. Ex. A at 5; Resp. Ex. C at 7; Resp. Ex. C Tab 2;⁹⁷ *see also* Resp. Ex. H at 1; Tr. 185-86. Because the wild virus contains several epitopes and antigens that are not included in the vaccine, the results of *Kridin et al.* could not be applied to HBV vaccination. Tr. 188-89; Resp. Ex. H at 2. Further, it was not clear to the authors whether the patients studied developed PV or the HBV infection first, making it impossible to analyze causation. Resp. Ex. A at 5. *Tavakolpour* discussed potential triggers for pemphigus, including vaccines, foods, stress, pesticides, and sun exposure, but Dr. Simpson argued that “no clear etiology has been established for these diseases.” Resp. Ex. C at 5; Resp. Ex. C Tab 12.⁹⁸ Finally, *Nikkels et al.* is irrelevant because it summarized skin reactions following several vaccinations and observed PV only after typhoid booster and flu vaccine. Resp. Ex. C at 7; Resp. Ex. C Tab 16;⁹⁹ Resp. Ex. C Tab 7;¹⁰⁰ Resp. Ex. C Tab 17;¹⁰¹ Resp. Ex. E at 2-3.

Dr. Simpson also referred to *Laniosz et al.*, which noted that “HBV vaccination is safe for immunosuppressed individuals” because it is not a live vaccine. Tr. 127-28; Resp. Ex. C Tab 11 at 3.¹⁰² He acknowledged that *Laniosz et al.* stated, “[r]arely, pemphigus and (childhood) pemphigoid have reportedly developed after hepatitis B immunization”, but he claimed the association was only temporal. Tr. 128; Resp. Ex. C Tab 11 at 4, citing Resp. Ex. C Tab 1.¹⁰³

Respondent’s experts’ central criticism was a lack of concrete evidence to support a causal link between the HBV vaccine and PV. They stated that large, case-controlled studies combining the results of multiple clinical studies carry more weight than case reports, which are “merely observations...that are hypothesis-generating rather than hypothesis-testing.” Resp. Ex. C at 7. As Dr. Simpson stated, “the pathogenesis of pemphigus is still under investigation and has not been robustly linked in a large-scale study to any particular exogenous factor, [thus] it is without solid scientific rationale to assert a causative link between the HBV vaccine and pemphigus based on a single published case report as has been alleged by Dr. Norris.” *Id.* at 7-8; Resp. Ex. C Tab 14;¹⁰⁴ Resp. Ex. E at 3; Resp. Ex. G at 2.

⁹⁵ Berkun et al., *supra* note 4.

⁹⁶ *Id.*

⁹⁷ Kridin et al., *supra* note 5.

⁹⁸ Tavakolpour, *supra* note 38.

⁹⁹ Nikkels et al., *supra* note 28.

¹⁰⁰ Bellaney & Rycroft, *supra* note 51.

¹⁰¹ Mignogna et al., *supra* note 66.

¹⁰² Laniosz et al., *supra* note 59.

¹⁰³ Berkun et al., *supra* note 4.

¹⁰⁴ Kasperkiewicz et al., *supra* note 61.

The lack of a definitive, established cause of PV does not defeat petitioner's claim. Petitioners in the Vaccine Program are not required to prove scientific certainty to meet their burden of proof. Given the rarity of PV, conceded to by Drs. Levinson and Simpson, and the state of current scientific knowledge, there is no way that a petitioner could satisfy such a high bar. Further, the Federal Circuit clearly stated that requiring "identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." See *Knudsen*, 35 F.3d at 549.

The lack of epidemiological evidence is similarly not dispositive. *Capizzano*, 440 F.3d at 1325-26 ("[r]equiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants."); see also *Althen*, 418 F.3d at 1280. While PV after the HBV vaccine is not documented in epidemiological studies, all experts agreed that PV is extremely rare, thus adding to the difficulty in capturing its presence in epidemiology.

Nevertheless, petitioner here has presented epidemiological evidence that supports his claim, albeit indirectly. Petitioner's experts both relied on *Kridin et al.*, which was an epidemiological study of nearly 2,000 patients with PV and nearly 10,000 controls. The authors found those with PV to have a higher prevalence of HBV infection when compared to controls, and their results were statistically significant. Tr. 12-13, 21-22, 49, 57, 89; Pet. Ex. 18;¹⁰⁵ Pet. Ex. 23 at 3, 4. Dr. Norris and Dr. Byers convincingly explained that the immune system responds similarly to vaccination and infection, as vaccinations contain some of the same epitopes that are present in the wild virus. Pet. Ex. 23 at 4; Tr. 57, 62-63, 89, 91. Accordingly, *Kridin et al.* supports an association between HBV vaccination and PV.

Further, the literature submitted in this case shows that PV is the result of genetic factors and environmental factors, such as vaccination. Pet. Ex. 15 at 2; Pet. Ex. 20 at 3; Resp. Ex. C at 5; Resp. Ex. E at 1. *Davidson & Diamond* noted that an environmental exposure is usually necessary to trigger autoreactivity, even in a genetically predisposed person. Pet. Ex. 21 at 4.¹⁰⁶ Discussing pemphigus specifically, *Kridin et al.* explained that "...pemphigus develops due to interaction between predisposing genetic and environmental factors." Pet. Ex. 18 at 1.¹⁰⁷

De Simone et al. provides further support for a link between vaccination and PV, as well as for petitioner's challenge-rechallenge theory. It is a case report of a patient who had flares of PV after receiving the flu vaccine. Pet. Ex. 19 at 1-2.¹⁰⁸ In discussing the subject of their case report, the authors noted that it "could be a mere coincidence" but "such strict time succession is clearly suspicious." *Id.* at 2. They also wrote that "[i]t is conceivable that relapses [of pemphigus] after immunization may be underdiagnosed. Stimulation of the immune system by a vaccine may disrupt the equilibrium achieved with [immunosuppressive] therapy." *Id.* Additionally, *De Simone et al.* discussed "exogenous factors that have been implicated in the pathogenesis or exacerbation

¹⁰⁵ *Kridin et al.*, *supra* note 5.

¹⁰⁶ *Davidson & Diamond*, *supra* note 23.

¹⁰⁷ *Kridin et al.*, *supra* note 5.

¹⁰⁸ *De Simone et al.*, *supra* note 6.

of pemphigus”, including medications, dietary factors, viruses, and vaccinations. *Id.* at 1.

Berkun et al. similarly stated that pemphigus is associated with antecedent factors like medication, infection, or vaccination. Pet. Ex. 17 at 1.¹⁰⁹ *Berkun et al.* was discussed by both parties as a case report of a patient who received the HBV vaccination and had an onset of PV symptoms three months later. *Id.*; see also Resp. Ex. C Tab 1 at 2. Dr. Simpson found it significant that there was a lapse of three months between vaccination and onset. Resp. Ex. A at 5. He noted the authors still recommended that PV patients receive non-live vaccines like HBV, which would be ill advised if HBV vaccine cross-reactivity was “an *established* factor in the pathogenesis of pemphigus or flaring of the disease.” Resp. Ex. C at 5; Resp. Ex. C Tab 1¹¹⁰ (emphasis added). While Dr. Simpson is correct to note that the HBV vaccine is not an “established” trigger of PV, *Berkun et al.* demonstrated a plausible link between the two. They discussed a patient who, much like petitioner here, had new onset PV with no antecedent factors apart from the HBV vaccination. Pet. Ex. 17 at 2. The authors also noted that the HBV vaccine is the “vaccine most often involved with autoimmunity . . . and its autoimmune side effects have been the subject of many studies in the last decade”. *Id.* Moreover, *Nikkels et al.* stated that “of all the anti-infective vaccinations, hepatitis vaccination is associated with the greatest variety of different skin reactions.” Resp. Ex. C Tab 16 at 6.¹¹¹

The authors of *Laniosz et al.*, submitted by Dr. Simpson, appeared to appreciate that the case reports of pemphigus following vaccination indicated some degree of risk of autoimmunity induced by vaccination. They wrote that “[i]mmunizations have been anecdotally reported to precede the development of immunobullous diseases. Because of the rarity and possible coincidental timing of these events, we did not weigh this heavily when developing the above guidelines. However, *these previous observations do underscore the complex interactions of protective immunity and autoimmunity.*” Resp. Ex. C Tab 11 at 6 (emphasis added).¹¹²

Petitioner submitted the more recent literature of *Masjedi et al.* and *Lee et al.* in support of petitioner’s experts’ theory that the hepatitis B vaccine induces a strong immune response that generates proinflammatory cytokines, such as IL-6 and tumor necrosis factor, that can activate the autoreactive B and T cells to become dysregulated and reactive against DSG 1 and 3. Tr. 11-12, 17-19; Pet. Ex. 20 at 2; Pet. Ex. 23 at 5. *Masjedi et al.* stated that the loss of adhesion between keratinocytes is induced by autoantibody production associated with both Th1 and Th2 derived cytokines. Pet. Ex. 45 at 1.¹¹³ Similarly, *Lee et al.* showed that “the role of T cells and cytokines in the pathogenesis [of pemphigus] is being increasingly recognized”. Pet. Ex. 44 at 1.¹¹⁴ Proinflammatory cytokines like IL-1, IL-8, and tumor necrosis factor are the likely key players in the coordination of the cellular and humoral response in pemphigus. *Id.* at 1-2, 3-4.

Solimani et al. provides further support for the proffered causal mechanism in this matter. *Solimani et al.* was a letter to the editor regarding a patient who developed PV following a Covid-

¹⁰⁹ Berkun et al., *supra* note 4.

¹¹⁰ *Id.*

¹¹¹ Nikkels et al., *supra* note 28.

¹¹² Laniosz et al., *supra* note 59.

¹¹³ Masjedi et al., *supra* note 7.

¹¹⁴ Lee et al., *supra* note 8.

19 (Pfizer) vaccine. Pet. Ex. 46 at 1.¹¹⁵ The authors noted the prior case reports that have shown PV following various vaccinations including Hepatitis B vaccine. *Id.* at 2, Table 1. Consistent with the opinions of all four experts in this matter, *Solimani et al.* recognized that the development of autoimmune diseases after vaccinations is rare, but “molecular mimicry, inflammatory dysregulation in genetically susceptible persons, epitope spreading or bystander activation seem to be involved in the onset of autoimmunity following vaccinations.” *Id.* at 2; Pet. Ex. 20 at 2-3; Pet. Ex. 23 at 3, 4; Resp. Ex. E at 1; Resp. Ex. F at 1. The authors explained that vaccinations boost B cell activity, resulting in a rapid increase in the memory B cells and antibody levels. *Id.* Further, *Lee et al.* noted that animal models show that both DSG-specific T cells and B cells are necessary for the production of pathogenic autoantibodies. Pet. Ex. 44 at 1.¹¹⁶

At hearing, Dr. Simpson conceded that pemphigus is rare and stated that “it is not surprising that there are rare reports of any known or suspected trigger.” Tr. 141. He further agreed that “[a]ny intervention . . . can have an adverse outcome, whether that’s an injection, a procedure, a vaccine, a medication”. Tr. 141-42. Dr. Levinson also agreed that PV is a rare disease. Tr. 198, 200. Likewise, Dr. Levinson conceded that “[a]nything can possibly do something”, although he then clarified that does not mean it is likely. Tr. 196.

Fortunately, adverse reactions to vaccines are rare, as is pemphigus. Nevertheless, adverse reactions do occur and so does pemphigus; and sometimes, pemphigus is the result of an adverse vaccine reaction. The literature filed in this matter supports petitioner’s causation theory, as well as the link between the hepatitis B vaccine and the onset of PV. As such, petitioner’s experts have provided a sound and reliable theory demonstrating by preponderant evidence that the HBV vaccine can cause the onset of pemphigus vulgaris in a genetically predisposed host, and petitioner has satisfied Prong I.

b. Prong II: Petitioner Has Provided a Logical Sequence of Cause and Effect

Under *Althen* prong two, petitioners must prove by a preponderance of the evidence that there is a “logical sequence of cause and effect showing that the vaccination was the reason for the injury.” *Capizzano*, 440 F.3d at 1324 (quoting *Althen*, 418 F.3d at 1278). “Petitioner[s] must show that the vaccine was the ‘but for’ cause of the harm . . . or in other words, that the vaccine was the ‘reason for the injury.’” *Pafford*, 451 F.3d at 1356 (internal citations omitted). However, petitioner does not need to eliminate alternative causes to establish a prima facie case. *Doe*, 601 F.3d at 1357-58.

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee’s treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326. Medical records are generally viewed as trustworthy evidence since they are created contemporaneously with treatment. *Cucuras*, 993 F.2d at 1528; *but see Kirby*, 993 F.3d at 1382-83. Petitioner need not make a specific type of evidentiary showing, i.e., “epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect.”

¹¹⁵ F. Solimani et al., *Development of Severe Pemphigus Vulgaris Following SARS-CoV-2 Vaccination with BNT162b2*, 35 J. OF THE EUR. ACAD. OF DERMATOLOGY AND VENEREOLOGY e649 (2021), filed as “Pet. Ex. 46”.

¹¹⁶ Lee et al., *supra* note 8.

Capizzano, 440 F.3d at 1325. Instead, petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. *Id.* at 1325-26.

Special Masters have previously held that challenge-rechallenge can serve as evidence supporting causation, specifically that the vaccine at issue did cause the injury alleged. *Capizzano*, 440 F.3d at 1322; *R.S. v. Sec’y of Health & Human Servs.*, No. 15-1207V, 2021 WL 6502227, at *14 (Fed. Cl. Spec. Mstr. Dec. 15, 2021).

In *Nussman*, the special master denied compensation in part because the petitioner’s theory regarding Prong II hinged on a finding of challenge-rechallenge, which he failed to prove. *Nussman v. Sec’y of Health & Human Servs.*, No. 99–500–V, 2008 WL 449656, at *12 n.6 (Fed. Cl. Spec. Mstr. Jan. 31, 2008) (“The challenge-rechallenge model is not a medical theory. The challenge-rechallenge paradigm is a method, based in logic, that can assist in proving that a vaccine caused an injury. As such, challenge-rechallenge is discussed in the second prong of *Althen*. The underlying logic can be used in a variety of disciplines, not just medicine.”); *aff’d*, 83 Fed. Cl. 111, 119-20 (2008) (upholding the special master’s finding that the petitioner did not have an adverse reaction to the initial vaccine, and thus, could not prove an initial “challenge”. Because the petitioner relied heavily, if not exclusively, on a challenge-rechallenge theory, he failed to prove a logical sequence of cause and effect.). More recently, though, the Court of Federal Claims upheld a special master’s Ruling on Entitlement where he found the petitioner satisfied Prong II based in part on a challenge-rechallenge theory. *Mager v. Sec’y of Health & Human Servs.*, 166 Fed. Cl. 414, 444-45 (2023).

These two cases are instructive on how challenge-rechallenge fits within the *Althen* analysis, showing that preponderant evidence of a challenge-rechallenge can support a finding that a petitioner demonstrated a logical sequence of cause and effect between the subject vaccine and the alleged injury. With this legal landscape in mind, challenge-rechallenge was discussed as both part of Prong I and Prong II in this case.

Well-established caselaw provides that the opinions and views of the petitioner’s treating physicians are entitled to weight, recognizing that treating physicians are likely in the best position to determine cause and effect between a particular trigger and an injury. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326. I find it significant that Dr. Norris, petitioner’s treating dermatologist, opined that petitioner’s PV was “suspected to be precipitated from hepatitis B vaccination” when he first started treating him. Pet. Ex. 4 at 30. Notably, Dr. Norris documented this opinion in the medical records roughly six months prior to the petition in this matter being filed, lending it even more weight since it was apparently not made in anticipation of any litigation but was rather solely related to petitioner’s treatment and medical care. *Id.*; see also Pet. Further, while a claim cannot be supported by a petitioner’s claims alone, petitioner’s statements here are entitled to some weight, particularly since petitioner is a medical doctor, who is board-certified in head and neck surgery. FH Tr. 5; §13(a)(1). Given his medical knowledge, he was in a unique position as a petitioner to note any exposures that may have been significant leading up to the onset of his PV. The only potential exposures he noted were the hepatitis B vaccines, and he recalled symptoms developing after each vaccination. FH Tr. 6-9, 11, 18-19, 21-22, 24, 33-36, 37-38, 47, 55-57, 58, 65 75-76, 77-78; Tr. 214, 216-17.

The medical records clearly show that petitioner experienced PV symptoms following the third HBV vaccine. Pet. Ex. 3 at 1-3 (dermatology records noting a chronic scalp rash and lesions on the right eye and the nose); Pet. Ex. 4 at 3 (dermatology records showing extensive lesions on petitioner's scalp, face, and chest); Pet. Ex. 7 at 9 (records from eye doctor documenting a sty and irritation of petitioner's right eye); Pet. Ex. 9 at 2 (dental records noting petitioner's gums to be tender and bleeding, and noting a tooth abscess and root canal). Lab results from September 16, 2015 showed high levels of autoantibodies of DSG 1 and 3, consistent with pemphigus. Pet. Ex. 1 at 13. Biopsies of petitioner's scalp, nose, and shoulder after the third vaccination were positive for PV. Pet. Ex. 3 at 1-3; Pet. Ex. 4 at 4, 16. Following the biopsies, petitioner was formally diagnosed with pemphigus vulgaris in August 2015, which Dr. Norris later confirmed due to the oral involvement of his symptoms and DSG 3 positivity. Pet. Ex. 1 at 13; Pet. Ex. 3 at 1-3; Pet. Ex. 4 at 22. All four experts agreed that PV is the appropriate diagnosis. Pet. Ex. 15 at 1, 3; Pet. Ex. 23 at 5-6; Resp. Ex. A at 3; Resp. Ex. C at 3.

Respondent disputed that petitioner's medical history was consistent with a challenge-rechallenge, arguing it was unclear from the records that petitioner suffered PV symptoms after the first and second HBV vaccines. Tr. 145-47. Respondent's experts argued that it was highly unlikely that petitioner would test negative for hepatitis antibodies while simultaneously producing anti-DSG antibodies that caused clinical PV lesions. Resp. Ex. G at 2. I agree with respondent's experts that the evidence is insufficient to show that the symptoms petitioner experienced after the first HBV vaccine were related to his PV, as confirmatory testing was not done, and petitioner did not have Hep B antibodies when he was tested in September 2014. Pet. Ex. 1 at 1.

However, consistent with petitioner's experts' opinions, I find that the evidence preponderates in favor of petitioner's development of PV symptoms after the second HBV vaccine. Although testing after the first vaccine failed to show antibodies to Hepatitis B, an antibody test was not done after petitioner's second HBV vaccine. Pet. Ex. 1 at 1, 9. Therefore, it is unknown whether petitioner had antibodies to Hepatitis B after the second HBV vaccination. The evidence supports petitioner's development of a shoulder lesion and rash after the second HBV, which he discussed with his colleague Dr. Massey. FH Tr. 6-7, 47; Pet. Ex. 6 at 1. Dr. Massey affirmed that, approximately two years prior—or around December 2014—petitioner asked him to look at a shoulder lesion that he thought may be cancerous. Pet. Ex. 12 at 1. They discussed doing a biopsy of the lesion which was never done because the lesion resolved on its own shortly thereafter. *Id.*; FH Tr. 6-7. Viewing the evidence as a whole petitioner's clinical course is consistent with a challenge-rechallenge, with the second HBV vaccine constituting the first challenge and the third HBV vaccine being a rechallenge. Dr. Norris convincingly explained that timing of onset can be evidence of causation when temporal proximity of symptoms repeats upon re-exposure to the same challenge. Tr. 84.

In addition to the evidence detailed above, I found petitioner's experts to be more credible. All experts in this case are well credentialled and highly regarded in their fields. However, the responses by both Dr. Levinson and Dr. Simpson when presented with "hypotheticals" that paralleled the facts in this case, as well as their refusal to agree that the facts here would at least raise suspicion that the HBV vaccine could be responsible for a patient's PV, reduced their credibility. It is worth noting that Dr. Levinson refused to answer a hypothetical related to a vaccine but immediately after entertained a hypothetical related to a medication. Tr. 208-10. Dr. Levinson

even conceded that he would consider not giving a particular medication to a patient who had adverse immunological responses to that medication in the past. Tr. 210.

Respondent argued that petitioner's HBV vaccinations did not cause his PV because HBV vaccination is not an established trigger of the disease.¹¹⁷ As explained at length in the prior section, preponderant evidence supports that the hepatitis B vaccine can trigger PV in a genetically predisposed person. Petitioner's medical history is consistent with the literature of PV following an environmental exposure like a vaccine or medication. Of particular relevance is *Berkun et al.*, which reported a patient who developed PV following his HBV vaccination. Pet. Ex. 17.¹¹⁸ Further, preponderant evidence shows that petitioner exhibited symptoms suggestive of and ultimately found to be PV following the second and third HBV vaccines, which supports petitioner's challenge-rechallenge theory and implicates the vaccinations as the trigger. Accordingly, petitioner has established Prong II.

c. Prong III: Petitioner Has Established a Proximate Temporal Relationship

Althen prong three requires petitioners to establish a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." *Id.* Petitioners must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under *Althen* prong one). *Id.*; *Koehn v. Sec'y of Health & Human Servs.*, 773 F.3d 1239, 1243 (Fed. Cir. 2014); *Shapiro*, 101 Fed. Cl. at 542; *see also Pafford*, 451 F.3d at 1358.

Petitioner submitted several articles that referenced the timing of symptom development following vaccination. *De Simone et al.* described a patient with PV who developed flares of the disease on two occasions, both of which followed flu vaccines. Pet. Ex. 19.¹¹⁹ The first PV flare was seven to ten days after a flu vaccine, and the second was seven days after a flu vaccine. *Id.* at 1-2. The authors noted that it "could be a mere coincidence", but "such strict time succession is clearly suspicious." *Id.* at 2. *Mignogna et al.* reported on a patient who developed newly onset PV one month after flu vaccination. Resp. Ex. C Tab 17.¹²⁰ Finally, the authors of *Berkun et al.* stated that "disease onset three months following [HBV] vaccination is appropriate for induction of immune response by the vaccine." Pet. Ex. 17 at 2.¹²¹ Based on the literature filed, preponderant evidence supports that symptoms of PV may develop anywhere from seven days to three months following HBV vaccination.¹²²

¹¹⁷ Respondent also argued that there are more likely triggers of petitioner's PV. Tr. 120, 123; Resp. Ex. C at 3, 5-6; Resp. Ex. E at 1; Resp. Ex. G at 2. As petitioner is not required to eliminate alternative causes to prove a prima facie case, alternative triggers are discussed separately below. *Doe*, 601 F.3d at 1357-58.

¹¹⁸ *Berkun et al.*, *supra* note 4.

¹¹⁹ *De Simone et al.*, *supra* note 6.

¹²⁰ *Mignogna et al.*, *supra* note 66.

¹²¹ *Berkun et al.*, *supra* note 4.

¹²² Petitioner's experts explained at length that the PV has an insidious onset because "there are defenses against this kind of thing happening". Tr. 71, 88. Here, it took a rechallenge to "really get the autoimmunity going". Tr. 30-31, 88. Thus, I find *Berkun et al.* to be probative in determining the appropriate onset of PV following a Hep B vaccine,

Respondent's experts did not necessarily refute petitioner's experts' opinions on timing. Rather, they argued that it is "sheer folly" to estimate how long it would take for the onset of PV after HBV vaccination since it has not been "established" that the vaccine can cause PV. Tr. 153-54; Resp. Ex. A at 6, 7; Resp. Ex. A Tab 3.¹²³ For the reasons detailed within the Prong I analysis, I do not find this argument persuasive.

Respondent's experts submitted that, generally, an immune response to immunization would take a few days to weeks—depending on whether it was the initial vaccination or a booster—to produce IgG antibodies, the types of antibodies necessary to cause PV. Resp. Ex. A at 5. Within a month of receiving the third HBV vaccine, petitioner began developing lesions on his head, eye, nose, and shoulder and developed a tooth abscess and gum bleeding. Pet. Ex. 3 at 1-3; Pet. Ex. 4 at 3; Pet. Ex. 7 at 9; Pet. Ex. 9 at 2. Although he was not formally diagnosed with PV until August 2015, all experts agreed that PV is a very difficult disease to diagnose due to the many ways and many locations in which it develops. Tr. 9, 92, 141; Pet. Ex. 1 at 13; Pet. Ex. 3 at 1-3; Pet. Ex. 4 at 4, 16; Pet. Ex. 15 at 1; Resp. Ex. C at 3. They also explained that PV is oftentimes not diagnosed for a long time after symptoms begin. Tr. 214-15. As concluded in the Fact Ruling, preponderant evidence supports that petitioner developed lesions in various locations including his mouth, eye, scalp, and nose within four weeks of receiving the third HBV vaccine. Ruling on Facts at 2, 13-14.

Furthermore, the evidence shows that petitioner developed a rash on his chest and lesion on his shoulder in slightly over one month after the second vaccine. Pet. Ex. 5 at 1; Pet. Ex. 12 at 1; FH Tr. 6-7. As such, petitioner's clinical course is consistent with the literature filed showing onset of PV seven days to three months following HBV vaccination. Pet. Ex. 19;¹²⁴ Resp. Ex. C Tab 17;¹²⁵ Pet. Ex. 17.¹²⁶ Notably, his course is also consistent with Dr. Levinson's opinion that it would take a few days to weeks to produce the antibodies necessary to cause PV. Resp. Ex. A at 5. He explained that the time it takes to produce antibodies is dependent on whether it is the first vaccine or a booster. *Id.* Here, the window during which time PV symptoms manifested shortened between the second and third HBV vaccines, with symptoms developing slightly over one month after the second HBV in October 2014 and within a month after the third vaccine in April 2015.

Accordingly, petitioner has preponderantly established a proximate temporal relationship between his HBV vaccinations and the onset of his PV, satisfying *Althen* Prong III.

C. Alternative Cause

Because the undersigned concludes that petitioner has established a prima facie case, petitioner is entitled to compensation unless respondent can put forth preponderant evidence "that [petitioner's] injury was in fact caused by factors unrelated to the vaccine." *Whitecotton v. Sec'y*

specifically in the context of a challenge-rechallenge. This finding is not intended to extend to the onset of autoimmune diseases following vaccination generally.

¹²³ Berkun et al., *supra* note 4.

¹²⁴ De Simone et al., *supra* note 6.

¹²⁵ Mignogna et al., *supra* note 66.

¹²⁶ *Id.*

of Health & Human Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), *rev'd on other grounds sub nom.*, *Shalala v. Whitecotton*, 514 U.S. 268 (1995); *see also Walther*, 485 F.3d at 1151.

Respondent's experts submitted several alternative causes for petitioner's PV, including lisinopril, tissue trauma, and infection. Dr. Levinson explained that pemphigus is associated with a number of medications including non-sulfhydryl drugs like lisinopril, with "the average incubation period between the start of the offending non-sulfhydryl ACE-inhibitor and the average onset of [PV] [being] 128 days". Resp. Ex. A at 4. Dr. Levinson argued that Dr. Byers dismissed lisinopril as a causal factor in this case and that she failed to appreciate that lisinopril was as viable a trigger as the HBV vaccination. Resp. Ex. H at 2.

It is irrelevant that lisinopril may in theory cause PV because the evidence shows that petitioner did not take the drug at any time near the subject vaccinations. Petitioner affirmed taking three doses of lisinopril in 2009, which made him dizzy and caused his blood pressure to drop too low, prompting him to discontinue it. Pet. Ex. 43 at 1. In 2015, when he already had "full-blown" PV, he took a single dose when his blood pressure was elevated from the pain of his PV. Tr. 212-13. That night, he developed palatal swelling and angioedema. He never took another dose and reported it so that it would be reflected in his medical records to ensure he would never be given it inadvertently in the future. Tr. 213; Pet. Ex. 43 at 1. Accordingly, I find that the three lisinopril petitioner took over three years prior to his first HBV vaccination was not a factor in his development of PV. The fourth pill was taken after he was diagnosed with PV; while he experienced side effects from the medication, he did not report an exacerbation of his PV.

The evidence also does not support respondent's argument that tissue trauma caused petitioner's PV. The records show that petitioner had a dental cleaning in February 2013—roughly two months after his first HBV vaccine—and the hygienist used only a hand tool due to heavy gingival bleeding to avoid trauma. Resp. Ex. C at 2, 6, 7; Pet. Ex. 9 at 1. Petitioner had no further dental issues with only some gum inflammation noted in August 2014 until the weeks following his third HBV vaccine when he developed painful, tender, and bleeding gums, a tooth abscess, and lesions on the right side of his mouth. Pet. Ex. 9 at 1-2.

Finally, respondent's experts pointed to shingles as an alternative cause of petitioner's PV. However, petitioner's records show that he reported a PV flare after suspected shingles in April 2017, well after he was diagnosed with PV. Resp. Ex. C at 6; Resp. Ex. E at 3; Pet. Ex. 14 at 11. Therefore, although shingles may have triggered a PV flare, it did not influence petitioner's development of PV years prior.

The undersigned disagrees with respondent's experts that there is evidence that lisinopril, dental issues, or shingles played any role in the onset of petitioner's PV as described above. As such, respondent has not met his burden in proving an alternative cause unrelated to the vaccine that was the "sole substantial factor" in petitioner's development of PV. *de Bazan*, 539 F.3d at 1354 (holding that Respondent's burden is to "identify[] a particular [unrelated] factor (or factors) and present[] sufficient evidence to establish that it was the sole substantial factor in bringing about the injury," thus "excluding the vaccine as a substantial factor"); *Deribeaux ex rel. Deribeaux v. Sec'y of Health & Human Servs.*, 105 Fed. Cl. 583, 595 (2012), *aff'd*, 717 F.3d 1363 (Fed. Cir. 2013); *Stone v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 233, 237 (2010); § 13(a)(1)(B).

V. Conclusion

For the reasons discussed above, the undersigned finds that petitioner has established by preponderant evidence that the second and third hepatitis B vaccinations caused his PV. Respondent failed to carry his burden in proving an alternative cause. Therefore, petitioner is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/ Mindy Michaels Roth

Mindy Michaels Roth
Special Master